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### CYCLIZATION PROCESS STEP IN THE MAKING OF QUINOLONES AND NAPHTHYRIDINES

#### FIELD OF THE INVENTION

The subject invention relates to processes for making quinolones and quinolone derivatives, which are compounds that are active antibacterial and/or are anti-HIV agents. The invention also relates to useful intermediates in making these compounds.

### **BACKGROUND OF THE INVENTION**

The chemical and medical literature describes compounds that are said to be antimicrobial, i.e., capable of destroying or suppressing the growth or reproduction of microorganisms, such as bacteria. For example, such antibacterials and other antimicrobials are described in <u>Antibiotics</u>, <u>Chemotherapeutics</u>, and <u>Antibacterial Agents for Disease Control</u> (M. Grayson, editor, 1982), and E. Gale et al., <u>The Molecular Basis of Antibiotic Action</u> 2d edition (1981).

The mechanism of action of these antibacterials vary. However, they are generally believed to function in one or more of the following ways: by inhibiting cell wall synthesis or repair; by altering cell wall permeability; by inhibiting protein synthesis; or by inhibiting synthesis of nucleic acids. For example, beta-lactam antibacterials act through inhibiting the essential penicillin binding proteins (PBPs) in bacteria, which are responsible for cell wall synthesis. As another example, quinolones act, at least in part, by inhibiting synthesis of DNA, thus preventing the cell from replicating.

The pharmacological characteristics of antimicrobials, and their suitability for any given clinical use, vary. For example, the classes of antimicrobials (and members within a class) may vary in 1) their relative efficacy against different types of microorganisms, 2) their susceptibility to development of microbial resistance and 3) their pharmacological characteristics, such as their bioavailability, and biodistribution. Accordingly, selection of an appropriate antibacterial (or other antimicrobial) in a given clinical situation requires analysis of many factors, including the type of organism involved, the desired method of administration, the location of the infection to be treated and other considerations.

Cyclization processes for making intermediate compounds useful in the synthesis of quinolone, naphthyridine, and related compounds are disclosed in a number of references including the following: European Patent Application No. 0 168,733 published January 22, 1986; and U.S. Patent No. 5,703,231 issued December 30, 1997. While the methods disclosed in the those publications represent useful advances in quinolone chemistry, Applicants have

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discovered that the use of certain leaving groups, not contemplated in those or other prior art references, in combination with the use of a silylating reactant provide several advantages relative to the processes disclosed in the prior art. For example, the present process allows the synthesis of various quinolones and related compounds by an intramolecular cyclization process in which the key leaving group on the starting aromatic ring precursor (depicted as XR<sup>9</sup> in Formula (A) below) is electron donating in nature. The aromatic ring precursor may contain other substituents which may be electron donating or electron withdrawing in nature. Certain prior cyclization methods to form quinolones disclose an electron withdrawing group as the leaving group on the starting aromatic ring and also may require the presence of other electron withdrawing groups at the ortho or para positions on that ring. See, e.g., U.S. Patent No. 5,703,231. Further, when other prior art has discussed the use of methoxy and thiomethyl leaving groups, reaction conditions disclosed are harsh insofar as they use sodium hydride and require high temperatures (140-160°C) in polar solvents.

The present process, in contrast, allows the use of a broader group of starting materials in the manufacture of quinolones, possibly leading to a more efficient and cost effective process. The process also allows the use of less harsh reaction conditions than the methods described in the art generally, which may also provide improved synthetic yields.

Accordingly, the present invention provides an improved means to obtain quinolones and derivatives of quinolones, which themselves may be active or may be intermediates for forming other active molecules.

#### SUMMARY OF THE INVENTION

The subject invention relates to a process for making a compound having a structure according to Formula (I), or an optical isomer, diastereomer or enantiomer thereof, or a pharmaceutically-acceptable salt, hydrate, or biohydrolyzable ester, amide or imide thereof:

$$R^{6}$$
 $R^{7}$ 
 $A$ 
 $R^{1}$ 
 $R^{2}$ 
 $R^{1}$ 
 $R^{2}$ 
 $R^{3}$ 

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the process comprising reacting one or more organosilicon reagents with a compound having a structure according to Formula (A):

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$$R^{6}$$
 $R^{7}$ 
 $A$ 
 $XR^{9}$ 
 $R^{1}$ 
 $H$ 
 $(A)$ 

wherein with regard to Formula (I) and Formula (A):

- (A) (1) A is N or C-R<sup>8</sup>, where R<sup>8</sup> is selected from hydrogen, alkyl, aryl, halo, a heterocyclic ring, amino, alkylamino, arylamino, alkoxy, nitro, cyano, aryloxy, esters of hydroxy, alkylthio, arylthio, aryloxy, esters of thio, alkylsulfonyl, arylsulfonyl, alkylphosphonyl, arylphosphonyl, alkylacyl, arylacyl, and aryl esters and amides of carboxy;
  - (2) R<sup>7</sup> is selected from hydrogen, alkyl, aryl, a heterocyclic ring, amino, alkylamino, arylamino, halo, nitro, cyano, alkoxy, aryloxy, esters of hydroxy, alkylthio, arylthio, esters of thio, alkylsulfonyl, arylsulfonyl, alkylphosphonyl, arylphosphonyl, alkylacyl, arylacyl, and alkyl and aryl esters and amides of carboxy;
  - (3) R<sup>6</sup> is selected from hydrogen, halo, alkyl, aryl, a heterocyclic ring, amino, alkylamino, arylamino, nitro, cyano, alkoxy, aryloxy, esters of hydroxy, alkylthio, arylthio, esters of thio, alkylsulfonyl, arylsulfonyl, alkylphosphonyl, arylphosphonyl, alkylacyl, arylacyl, and alkyl and aryl esters and amides of carboxy;
  - (4) R<sup>5</sup> is selected from hydrogen, alkyl, aryl, cyano, a heterocyclic ring, amino, alkylamino, arylamino, alkylacyl, arylacyl, and aryl esters and amides of carboxy;
  - (5) R<sup>1</sup> is selected from a carbocyclic ring, a heterocyclic ring, lower alkyl, lower alkene, lower alkyne and -CH(R<sup>10</sup>)(R<sup>11</sup>) where R<sup>10</sup> is selected from lower alkyl and phenyl and R<sup>11</sup> is -CH<sub>2</sub>Y(O=)CR<sup>12</sup> where R<sup>12</sup> is selected from lower alkyl and phenyl and Y is selected from -NH-, -O- and -S-;
  - (6) R<sup>2</sup> is selected from hydrogen, alkyl, aryl, a heterocyclic ring, alkylthio and arylthio; and
     (7) R<sup>3</sup> is selected from hydrogen, alkoxy, aryloxy, alkyl and aryl; or
- (B) R<sup>1</sup> and R<sup>2</sup> can join to form a 5- or 6-membered carbocyclic or heterocyclic ring, where A, R<sup>3</sup>, R<sup>5</sup>, R<sup>6</sup>, R<sup>7</sup> and R<sup>8</sup>, if present, are as described in (A); or
- 25 (C) R<sup>6</sup> and R<sup>7</sup> can join to form a 5- or 6-membered carbocyclic or heterocyclic ring, where A, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>5</sup> and R<sup>8</sup>, if present, are as described in (A);

and wherein with regard to Formula (A):

(D) X is selected from -O- and -S- and R<sup>9</sup> is selected from C<sub>1</sub>-C<sub>10</sub> alkyl, aryl and heteroaryl.

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The compounds of Formula (I) may themselves be effective antimicrobial or anti-HIV agents, or they may be further reacted using well known chemistry to provide a molecule having antimicrobial or anti-HIV activity. As such, the compounds of Formula (I) may be useful intermediates in the formation of other active quinolones and quinolone derivatives.

The invention also relates to novel intermediates, having a structure of Formula (A), that are useful in the present process.

#### DETAILED DESCRIPTION OF THE INVENTION

#### I. Terms and Definitions:

The following is a list of definitions for terms used herein:

"Acyl" or "carbonyl" is a radical formed by removal of the hydroxy from a carboxylic acid (i.e., R-C(=O)-). "Alkylacyl" is -C(=O)-alkyl and "Arylacyl is -C(=O)-aryl. Preferred acyl groups include (for example) acetyl, formyl, and propionyl.

"Alkyl" is a saturated hydrocarbon chain having 1 to 15 carbon atoms, preferably 1 to 10, more preferably 1 to 4 carbon atoms. "Alkene" is a hydrocarbon chain having at least one (preferably only one) carbon-carbon double bond and having 2 to 15 carbon atoms, preferably 2 to 10, more preferably 2 to 4 carbon atoms. "Alkyne" is a hydrocarbon chain having at least one (preferably only one) carbon-carbon triple bond and having 2 to 15 carbon atoms, preferably 2 to 10, more preferably 2 to 4 carbon atoms. Alkyl, alkene and alkyne chains (referred to collectively as "hydrocarbon chains") may be straight or branched and may be unsubstituted or substituted. Preferred branched alkyl, alkene and alkyne chains have one or two branches, preferably one branch. Preferred chains are alkyl. Alkyl, alkene and alkyne hydrocarbon chains each may be unsubstituted or substituted with from 1 to 4 substituents; when substituted, preferred chains are mono-, di-, or tri-substituted. Alkyl, alkene and alkyne hydrocarbon chains each may be substituted with halo, hydroxy, aryloxy (e.g., phenoxy), heteroaryloxy, acyloxy (e.g., acetoxy), carboxy, aryl (e.g., phenyl), heteroaryl, cycloalkyl, heterocycloalkyl, spirocycle, amino, amido, acylamino, keto, thioketo, cyano, or any combination thereof. Preferred hydrocarbon groups include methyl, ethyl, propyl, isopropyl, butyl, vinyl, allyl, butenyl, and exomethylenyl.

"Alkoxy" is an oxygen radical having a hydrocarbon chain substituent, where the hydrocarbon chain is an alkyl or alkenyl (i.e., -O-alkyl or -O-alkenyl) that is unsubstituted or substituted as described above. In the case of substituted alkoxy, preferred substituents include

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1-5 fluorine atoms. Preferred alkoxy groups include (for example) methoxy, di-fluoro methoxy, ethoxy, penta-fluoro ethoxy, propoxy and allyloxy.

Also, as referred to herein, a "lower" alkoxy, alkyl, alkene or alkyne moiety (e.g., "lower alkyl") is a chain comprised of 1 to 6, preferably from 1 to 4, carbon atoms in the case of alkyl and alkoxy, and 2 to 6, preferably 2 to 4, carbon atoms in the case of alkene and alkyne.

"Alkylphosphonyl" is -PO3-alkyl (e.g. -PO3-CH3).

"Alkylsulfonyl" is -SO<sub>2</sub>-alkyl (e.g., -SO<sub>2</sub>-CH<sub>3</sub>).

"Alkylthio" is -S-alkyl (e.g. -S-CH<sub>3</sub>).

"Amino" refers to -NH<sub>2</sub>. "Alkylamino" is an amino substituted with at least one alkyl moiety (e.g., -NH(CH<sub>3</sub>). "Arylamino" is an amino substituted with at least one aryl moiety (e.g., -NH(C<sub>6</sub>H<sub>5</sub>).

"Aryl" is an aromatic hydrocarbon ring. Aryl rings are monocyclic or fused bicyclic ring systems. Monocyclic aryl rings contain 6 carbon atoms in the ring. Monocyclic aryl rings are also referred to as phenyl rings. Bicyclic aryl rings contain from 8 to 17 carbon atoms, preferably 9 to 12 carbon atoms, in the ring. Bicyclic aryl rings include ring systems wherein one ring is aryl and the other ring is aryl, cycloalkyl, or heterocycloakyl. Preferred bicyclic aryl rings comprise 5-, 6- or 7-membered rings fused to 5-, 6-, or 7-membered rings. Aryl rings may be unsubstituted or substituted with from 1 to 4 substituents on the ring. Aryl may be substituted with halo, cyano, nitro, hydroxy, carboxy, amino, acylamino, alkyl, heteroalkyl, haloalkyl, phenyl, aryloxy, alkoxy, heteroalkyloxy, carbamyl, haloalkyl, methylenedioxy, heteroaryloxy, or any combination thereof. Preferred aryl rings include naphthyl, tolyl, xylyl, and phenyl. The most preferred aryl ring radical is phenyl.

"Aryloxy" is an oxygen radical having an aryl substituent (i.e., -O-aryl). Preferred aryloxy groups include (for example) phenoxy, napthyloxy, methoxyphenoxy, and methylenedioxyphenoxy.

"Arylphosphonyl" is -PO<sub>3</sub>-aryl (e.g., - PO<sub>3</sub>- $C_6H_5$ ).

"Arylsulfonyl" is -SO<sub>2</sub>-aryl (e.g., -SO<sub>2</sub>-C<sub>6</sub>H<sub>5</sub>).

"Arylthio" is -S-aryl (e.g., -S-C<sub>6</sub>H<sub>5</sub>).

"Biohydrolyzable amides" are aminoacyl, acylamino, or other amides of the compounds of the invention, where the amide does not essentially interfere, preferably does not interfere, with the activity of the compound, or where the amide is readily converted in vivo by a host to yield an active compound.

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"Biohydrolyzable imides" are imides of compounds of the invention, where the imide does not essentially interfere, preferably does not interfere, with the activity of the compound, or where the imide is readily converted in vivo by a host to yield an active compound. Preferred imides are hydroxyimides.

"Biohydrolyzable esters" are esters of compounds of the invention, where the ester does not essentially interfere, preferably does not interfere, with the antimicrobial activity of the compound, or where the ester is readily converted in a host to yield an active compound. Many such esters are known in the art, as described in U.S. Patent No. 4,783,443, issued to Johnston and Mobashery on November 8, 1988 (incorporated by reference herein). Such esters include lower alkyl esters, lower acyloxy-alkyl esters (such as acetoxymethyl, acetoxyethyl, aminocarbonyloxymethyl, pivaloyloxymethyl and pivaloyloxyethyl esters), lactonyl esters (such as phthalidyl and thiophthalidyl esters), lower alkoxyacyloxyalkyl esters (such as methoxycarbonyloxymethyl, ethoxycarbonyloxyethyl and isopropoxycarbonyloxyethyl esters), alkoxyalkyl esters, choline esters and alkylacylaminoalkyl esters (such as acetamidomethyl esters).

"Carbocyclic ring" encompasses both cycloalkyl and aryl moieties, as those terms are defined herein.

"Carbonyl" is -C(=O)-.

"Cycloalkyl" is a saturated or unsaturated hydrocarbon ring. Cycloalkyl rings are not aromatic. Cycloalkyl rings are monocyclic, or are fused, spiro, or bridged bicyclic ring systems. Monocyclic cycloalkyl rings contain from about 3 to about 9 carbon atoms, preferably from 3 to 7 carbon atoms, in the ring. Bicyclic cycloalkyl rings contain from 7 to 17 carbon atoms, preferably from 7 to 12 carbon atoms, in the ring. Preferred bicyclic cycloalkyl rings comprise 4-, 5-, 6- or 7-membered rings fused to 5-, 6-, or 7-membered rings. Cycloalkyl rings may be unsubstituted or substituted with from 1 to 4 substituents on the ring. Cycloalkyl may be substituted with halo, cyano, alkyl, heteroalkyl, haloalkyl, phenyl, keto, hydroxy, carboxy, amino, acylamino, aryloxy, heteroaryloxy, or any combination thereof. Preferred cycloalkyl rings include cyclopropyl, cyclopentyl, and cyclohexyl.

"Halo" or "halogen" is fluoro, chloro, bromo or iodo. Preferred halo are fluoro, chloro and bromo; more preferred typically are chloro and fluoro, especially fluoro.

"Haloalkyl" is a straight, branched, or cyclic hydrocarbon substituted with one or more halo substituents. Preferred are C<sub>1</sub>-C<sub>12</sub> haloalkyls; more preferred are C<sub>1</sub>-C<sub>6</sub> haloalkyls; still

more preferred still are  $C_1$ - $C_3$  haloalkyls. Preferred halo substituents are fluoro and chloro. The most preferred haloalkyl is trifluoromethyl.

"Heteroatom" is a nitrogen, sulfur, or oxygen atom. Groups containing more than one heteroatom may contain different heteroatoms.

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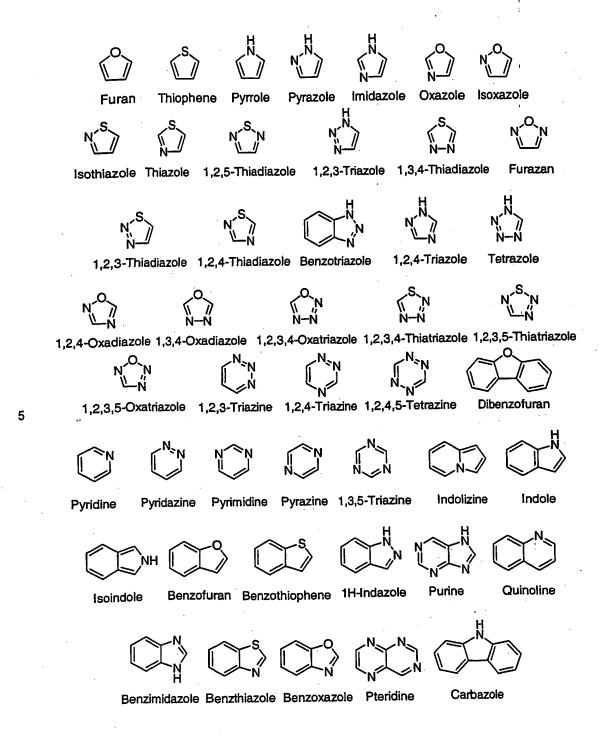
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"Heteroalkyl" is a saturated or unsaturated chain containing carbon and at least one heteroatom, wherein no two heteroatoms are adjacent. Heteroalkyl chains contain from 2 to 15 member atoms (carbon and heteroatoms) in the chain, preferably 2 to 10, more preferably 2 to 5. For example, alkoxy (i.e., -O-alkyl or -O-heteroalkyl) radicals are included in heteroalkyl. Heteroalkyl chains may be straight or branched. Preferred branched heteroalkyl have one or two branches, preferably one branch. Preferred heteroalkyl are saturated. Unsaturated heteroalkyl have one or more carbon-carbon double bonds and/or one or more carbon-carbon triple bonds. Preferred unsaturated heteroalkyls have one or two double bonds or one triple bond, more preferably one double bond. Heteroalkyl chains may be unsubstituted or substituted with from 1 to 4 substituents. Preferred substituted heteroalkyl are mono-, di-, or tri-substituted. Heteroalkyl may be substituted with lower alkyl, haloalkyl, halo, hydroxy, aryloxy, heteroaryloxy, acyloxy, carboxy, monocyclic aryl, heteroaryl, cycloalkyl, heterocycloalkyl, spirocycle, amino, acylamino, amido, keto, thioketo, cyano, or any combination thereof.

"Heteroaryl" is an aromatic ring containing carbon atoms and from 1 to about 6 heteroatoms in the ring. Heteroaryl rings are monocyclic or fused bicyclic ring systems. Monocyclic heteroaryl rings contain from about 5 to about 9 member atoms (carbon and heteroatoms), preferably 5 or 6 member atoms, in the ring. Bicyclic heteroaryl rings contain from 8 to 17 member atoms, preferably 8 to 12 member atoms, in the ring. Bicyclic heteroaryl rings include ring systems wherein one ring is heteroaryl and the other ring is aryl, heteroaryl, cycloalkyl, or heterocycloalkyl. Preferred bicyclic heteroaryl rings systems comprise 5-, 6- or 7-membered rings fused to 5-, 6-, or 7-membered rings. Heteroaryl rings may be unsubstituted or substituted with from 1 to 4 substituents on the ring. Heteroaryl may be substituted with halo, cyano, nitro, hydroxy, carboxy, amino, acylamino, alkyl, heteroalkyl, haloalkyl, phenyl, alkoxy, aryloxy, heteroaryloxy, or any combination thereof. Preferred heteroaryl rings include, but are not limited to, the following:



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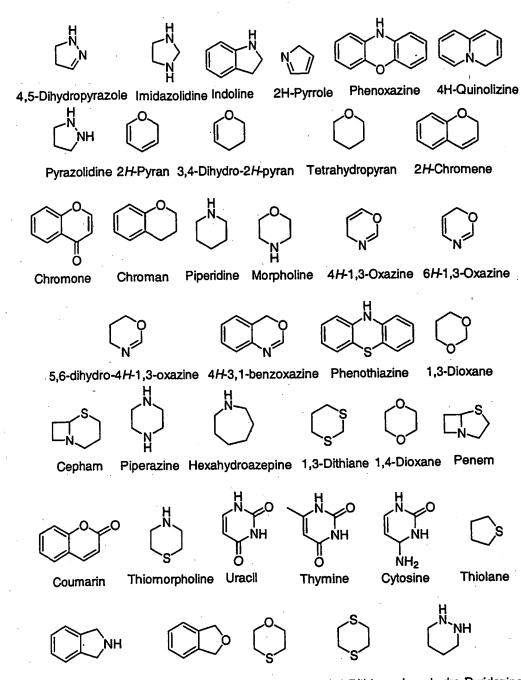
"Heteroaryloxy" is an oxygen radical having a heteroaryl substituent (i.e., -O-heteroaryl). Preferred heteroaryloxy groups include (for example) pyridyloxy, furanyloxy, (thiophene)oxy, (oxazole)oxy, (thiazole)oxy, (isoxazole)oxy, pyrmidinyloxy, pyrazinyloxy, and benzothiazolyloxy.

"Heterocycloalkyl" is a saturated or unsaturated ring containing carbon atoms and from 1 to about 4 (preferably 1 to 3) heteroatoms in the ring. Heterocycloalkyl rings are not aromatic. Heterocycloalkyl rings are monocyclic or bicyclic ring systems. Monocyclic heterocycloalkyl rings contain from about 3 to about 9 member atoms (carbon and heteroatoms), preferably from 5 to 7 member atoms, in the ring. Bicyclic heterocycloalkyl rings contain from 7 to 17 member atoms, preferably 7 to 12 member atoms, in the ring. Bicyclic heterocycloalkyl rings contain from about 7 to about 17 ring atoms, preferably from 7 to 12 ring atoms. Bicyclic heterocycloalkyl rings may be fused, spiro, or bridged ring systems. Preferred bicyclic heterocycloalkyl rings comprise 5-, 6- or 7-membered rings fused to 5-, 6-, or 7-membered rings. Heterocycloalkyl rings may be unsubstituted or substituted with from 1 to 4 substituents on the ring. Heterocycloalkyl may be substituted with halo, cyano, hydroxy, carboxy, keto, thioketo, amino, acylamino, acyl, amido, alkyl, heteroalkyl, haloalkyl, phenyl, alkoxy, aryloxy or any combination thereof. Preferred substituents on heterocycloalkyl include halo and haloalkyl. Preferred heterocycloalkyl rings include, but are not limited to, the following:

Do	DNH	Ľ	□NH	$\bigcirc$		N
Oxirane	Aziridine	Oxetane	Azetidine	Tetrahydrofuran	Pyrrolidine	3H-Indole
	C <sup>s</sup>	s	\s\s\	C <sub>0</sub> N		NH

1,3-Dioxolane 1,2-Dithiolane 1,3-Dithiolane 4,5-Dihydroisoxazole 2,3-Dihydroisoxazole

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2,3-Dihydro-1 H-Isoindole Phthalan 1,4-Oxathiane 1,4-Dithiane hexahydro-Pyridazine

1,2-Benzisothiazoline Benzylsultam

"Heterocyclic ring" encompasses both heterocycloalkyl and heteroaryl moieties, as those terms are defined herein.

"Host" is a substrate capable of sustaining a microbe, preferably it is a living organism, more preferably an animal, more preferably a mammal, more preferably still a human.

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The terms "optical isomer", "stereoisomer", and "diastereomer" have the standard art recognized meanings (see, e.g., <u>Hawley's Condensed Chemical Dictionary</u>, 11th Ed.). The illustration of specific protected forms and other derivatives of the compounds of the instant invention is not intended to be limiting. The application of other useful protecting groups, salt forms, etc. is within the ability of the skilled artisan.

The compounds of the invention may have one or more chiral centers. As a result, one may selectively prepare one optical isomer, including diastereomer and enantiomer, over another, for example by use of chiral starting materials, catalysts or solvents, one may prepare both stereoisomers or both optical isomers, including diastereomers and enantiomers at once (a racemic mixture). Since the compounds of the invention may exist as racemic mixtures, mixtures of optical isomers, including diastereomers and enantiomers, or stereoisomers, they may be separated using known methods, such as chiral resolution, chiral chromatography and the like.

In addition, it is recognized that one optical isomer, including diastereomer and enantiomer, or stereoisomer may have favorable properties over the other. Thus when disclosing and claiming the invention, when one racemic mixture is disclosed, it is clearly contemplated that both optical isomers, including diastereomers and enantiomers, or stereoisomers substantially free of the other are disclosed and claimed as well.

An "organosilicon reagent" is any silicon-containing reagent that is commonly utilized in silylation reactions, that is, reactions which substitute a hydrogen atom bound to a heteroatom (e.g., -OH, =NH, -SH, etc.) with a silyl group, usually a trialkylsilyl group, including reactions of a tautomer of a heteroatom system to form a silyl derivative (e.g., silyl emol ethers), thus forming a silicon-heteroatom bond. Many such compounds are known in the art, as described in the following articles: E. Plueddemann, "Silylating Agents", in: Kirk-Othmer, 3d ed., Vol. 20, "Encyclopedia of Chemical Technology" (1982); I. Fleming, "Organic Silicon Chemistry", in: Vol. 3, "Comprehensive Organic Chemistry" (D. Jones, editor, 1979); B. Cooper, "Silylation in Organic Synthesis", Proc. Biochem 9 (1980); B. Cooper, "Silylation as a Protective Method in Organic Synthesis", Chem. Ind. 794 (1978); J. Rasmussen, "O-Silylated Enolates—Versatile Intermediates for Organic Synthesis" 91 Synthesis (1977). Representative organosilicon reagents

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useful in the present process include, but are not limited to, chlorotrimethylsilane, N,O-1,3-N.O-bis(trimethylsilyl)trifluoroacetamide, bis(trimethylsilyl)acetamide, 1,1,1,3,3,3-hexamethyldisilazane, N-methyl-Nbis(trimethylsilyl)urea, trimethylsilyl 1-trimethylsilylimidazole, trimethylsilyltrifluoroacetamide, trifluoromethanesulfonate, tert-butyldimethylchlorosilane, 1-(tert-butyldimethylsilyl)imidazole, N-tert-butyldimethyl-N-methyltrifluoroacetamide, ethyl(trimethylsilyl)acetate, trifluoromethanesulfonate, tert-butyldiphenylchlorosilane, tert-butylbutyldimethylsilyl dimethylphenylchlorosilane, triethylchlorosilane, triethylsilyl methoxyphenylbromosilane, trifluoromethane-sulfonate, and triphenylchlorosilane. Of the various organosilicon reagents useful herein, N,O-bis(trimethylsilyl)acetamide, N,O-bis(trimethylsilyl)trifluoroacetamide, Nmethyl-N-trimethylsilyltrifluoroacetamide and tert-butyldiphenylchlorosilane are particularly preferred. More than one organosilicon reagent may be used in the present process.

A "pharmaceutically-acceptable salt" is a cationic salt formed at any acidic (e.g., carboxyl) group, or an anionic salt formed at any basic (e.g., amino, alkylamino, dialkylamino, morphylino, and the like) group on the compound of the invention. Since many of the compounds of the invention are zwitterionic, either salt is possible and acceptable. Many such salts are known in the art. Preferred cationic salts include the alkali metal salts (such as sodium and potassium), alkaline earth metal salts (such as magnesium and calcium) and organic salts, such as ammonio. Preferred anionic salts include halides, sulfonates, carboxylates, phosphates, and the like. Clearly contemplated in such salts are addition salts that may provide an optical center, where once there was none. For example, a chiral tartrate salt may be prepared from the compounds of the invention, and this definition includes such chiral salts. Salts contemplated are nontoxic in the amounts administered to the patient-animal, mammal or human.

The compounds made by the present process may be sufficiently basic to form acid-addition salts. The compounds are useful both in the free base form and the form of acid-addition salts, and both forms are within the purview of the invention. The acid-addition salts are in some cases a more convenient form for use. In practice, the use of the salt form inherently amounts to the use of the base form of the active. Acids used to prepare acid-addition salts include preferably those which produce, when combined with the free base, medicinally acceptable salts. These salts have anions that are relatively innocuous to the animal organism, such as a mammal, in medicinal doses of the salts so that the beneficial property inherent in the free base are not vitiated by any side effects ascribable to the acid's anions.

Examples of appropriate acid-addition salts include, but are not limited to hydrochloride, hydrobromide, hydroiodide, sulfate, hydrogensulfate, acetate, trifluoroacetate, nitrate, citrate, fumarate, formate, stearate, succinate, maleate, malonate, adipate, glutarate, lactate, propionate, butyrate, tartrate, methanesulfonate, trifluoromethanesulfonate, p-toluenesulfonate, dodecyl sulfate, cyclohexanesulfamate, and the like. However, other appropriate medicinally acceptable salts within the scope of the invention are those derived from other mineral acids and organic acids. The acid-addition salts of the basic compounds are prepared by several methods. For example, the free base can be dissolved in an aqueous alcohol solution containing the appropriate acid and the salt is isolated by evaporation of the solution. Alternatively, they may be prepared by reacting the free base with an acid in an organic solvent so that the salt separates directly. Where separation of the salt is difficult, it can be precipitated with a second organic solvent, or can be obtained by concentration of the solution.

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Although medicinally acceptable salts of the basic compounds are preferred, all acid-addition salts are within the scope of the present invention. All acid-addition salts are useful as sources of the free base form, even if the particular salt per se is desired only as an intermediate product. For example, when the salt is formed only for purposes of purification or identification, or when it is used as an intermediate in preparing a medicinally acceptable salt by ion exchange procedures, these salts are clearly contemplated to be a part of this invention.

Such salts are well understood by the skilled artisan, and the skilled artisan is able to prepare any number of salts given the knowledge in the art. Furthermore, it is recognized that the skilled artisan may prefer one salt over another for reasons of solubility, stability, formulation ease and the like. Determination and optimization of such salts is within the purview of the skilled artisan's practice.

As used herein, a "quinolone derivative" includes prodrugs of a quinolone, or an active drug made from a quinolone. Preferably, such derivatives include lactams (e.g., cephems, carbacephems, penems, monolactams, etc.) covalently linked to the quinolone optionally via a spacer. Such derivatives and methods to make and use them are apparent to the skilled artisan, given the teachings of this specification.

"Spirocycle" is an alkyl or heteroalkyl diradical substituent of alkyl or heteroalkyl wherein said diradical substituent is attached germinally and wherein said diradical substituent forms a ring, said ring containing 4 to 8 member atoms (carbon or heteroatom), preferably 5 or 6 member atoms.

A "solvate" is a complex formed by the combination of a solute (e.g., a quinolone) and a solvent (e.g., water). See J. Honig et al., The Van Nostrand Chemist's Dictionary, p. 650 (1953). Pharmaceutically-acceptable solvents used according to this invention include those that do not interfere with the biological activity of the quinolone (e.g., water, ethanol, acetic acid, N,N-dimethylformamide and others known or readily determined by the skilled artisan).

While alkyl, heteroalkyl, cycloalkyl, and heterocycloalkyl groups may be substituted with hydroxy, amino, and amido groups as stated above, the following are not envisioned in the invention:

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- 1. Enols (OH attached to a carbon bearing a double bond).
- 2. Amino groups attached to a carbon bearing a double bond (except for vinylogous amides).
- 3. More than one hydroxy, amino, or amido attached to a single carbon (except where two nitrogen atoms are attached to a single carbon atom and all three atoms are member atoms within a heterocycloalkyl ring).

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- 4. Hydroxy, amino, or amido attached to a carbon that also has a heteroatom attached to it.
- 5. Hydroxy, amino, or amido attached to a carbon that also has a halogen attached to it.

The illustration of the use of specific protected forms and other derivatives of the Formula 1 compounds in the present process are not intended to be limiting. The application of other useful protecting groups, salt forms, etc. is within the ability of the skilled artisan.

## II. Preferred Compounds Made By the Subject Process:

The subject invention relates to a process comprising the following process step:

Formula (A)

Formula (I)

where R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>5</sup>, R<sup>6</sup>, R<sup>7</sup>, A, X and R<sup>9</sup> are as defined in the Summary of the Invention section above.

With reference to Formula (I) and Formula (A), the description above indicates that in one embodiment (defined in sub-part (A)), the nucleus of the final compounds of Formula (I) will include two fused rings as depicted. Alternatively, the nucleus of the Formula (I) compounds will, upon cyclization via the present process, include three fused rings, as defined in sub-parts (B) and (C). These alternative embodiments are depicted as Formula (B) and Formula (C), respectively, below.

In the above structures,  $R^5$  is selected from hydrogen, alkyl, aryl, cyano, a heterocyclic ring, amino, alkylamino, arylamino, alkylacyl, arylacyl, and aryl esters and amides of carboxy. Preferred  $R^5$  is selected from hydrogen,  $C_1$  to about  $C_4$  alkyl, phenyl, amino and  $C_1$  to about  $C_4$  mono- or dialkylamino. More preferred  $R^5$  is selected form hydrogen, amino, methyl, ethyl, methylamino and dimethylamino. Alkyl and aryl portions of the  $R^5$  moieties are preferably unsubstituted or substituted with fluoro.

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In the above structures, R<sup>6</sup> is selected from hydrogen, halo, alkyl, aryl, a heterocyclic ring, amino, alkylamino, arylamino, nitro, cyano, alkoxy, aryloxy, esters of hydroxy, alkylthio, arylthio, esters of thio, alkylsulfonyl, arylsulfonyl, alkylphosphonyl, arylphosphonyl, alkylacyl, arylacyl, and alkyl and aryl esters and amides of carboxy. Preferred R<sup>6</sup> is selected from hydrogen, halo, nitro, C<sub>1</sub> to about C<sub>4</sub> alkylamino, C<sub>1</sub> to about C<sub>4</sub> alkoxy, and C<sub>1</sub> to about C<sub>4</sub> esters of hydroxy. More preferred R<sup>6</sup> is selected from hydrogen, fluoro, chloro, methyl, methylamino, dimethylamino, nitro, methoxy and acetoxy. Alkyl and aryl portions of the R<sup>6</sup> moieties are preferably unsubstituted or substituted with fluoro.

In the above structures, R<sup>7</sup> is selected from hydrogen, alkyl, aryl, a heterocyclic ring, amino, alkylamino, arylamino, halo, nitro, cyano, alkoxy, aryloxy, esters of hydroxy, alkylthio, arylthio, esters of thio, alkylsulfonyl, arylsulfonyl, alkylphosphonyl, arylphosphonyl, alkylacyl, arylacyl, and alkyl and aryl esters and amides of carboxy. Preferred R<sup>7</sup> is selected from hydrogen, halo, nitro, C<sub>1</sub> to about C<sub>4</sub> alkyl, unsubstituted amino, C<sub>1</sub> to about C<sub>4</sub> mono- or di-alkylamino, phenyl, naphthyl, a heterocyclic ring having one ring with 5 or 6 ring atoms or two fused rings with 8-10 ring atoms, C<sub>1</sub> to about C<sub>4</sub> alkylthio, phenylthio, phenoxy and C<sub>1</sub> to about C<sub>4</sub> esters of hydroxy. More preferred R<sup>7</sup> is selected from hydrogen, fluoro, chloro, bromo, nitro, unsubstituted amino, methylamino, dimethylamino and trifluoroacetoxy. Alkyl and aryl portions of the R<sup>7</sup> moieties are preferably unsubstituted or substituted with one or more fluoro atoms.

In the above structures, A is N or C-R<sup>8</sup>, preferably C-R<sup>8</sup>. R<sup>8</sup> is selected from hydrogen, alkyl, aryl, halo, a heterocyclic ring, amino, alkylamino, arylamino, alkoxy, nitro, cyano, aryloxy,

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esters of hydroxy, alkylthio, arylthio, esters of thio, alkylsulfonyl, arylsulfonyl, alkylphosphonyl, arylphosphonyl, alkylacyl, arylacyl, and aryl esters and amides of carboxy. Preferred  $R^8$  is selected form hydrogen, halo, about  $C_1$ - $C_4$  alkyl, phenyl, about  $C_1$ - $C_4$  alkoxy, about  $C_1$ - $C_4$  alkylthio, and phenoxy. More preferred  $R^8$  is selected from hydrogen, fluoro, chloro, methoxy, di- and trifluoromethoxy, methylthio, di- and trifluoromethylthio, methyl, ethyl, cyclopropyl and phenyl.

In the above structures,  $R^1$  is selected from a carbocyclic ring, a heterocyclic ring, lower alkyl, lower alkene, lower alkyne, and  $-CH(R^{10})(R^{11})$  where  $R^{10}$  is selected from lower alkyl and phenyl and  $R^{11}$  is  $-CH_2Y(O=)CR^{12}$  where  $R^{12}$  is selected from lower alkyl and phenyl and Y is selected from -NH-, -O- and -S-. Preferred  $R^1$  is selected from  $C_1$ - $C_4$  alkyl,  $C_3$ - $C_6$  cycloalkyl and aryl. More preferred  $R^1$  is selected from cyclopropyl, ethyl, 2,4-difluorophenyl, 2-methyl-1-acetoxypropane, 2-methyl-1-thioacetoxypropane. Akyl, cycloalkyl and aryl portions of the  $R^1$  moieties are preferably unsubstituted or substituted with fluoro.

In the above structures,  $R^2$  is selected from hydrogen, alkyl, aryl, a heterocyclic ring, alkylthio and arylthio. Preferred  $R^2$  is selected from hydrogen,  $C_1$ - $C_4$  alkyl,  $C_1$ - $C_4$  alkylthio and phenyl. More preferred  $R^2$  is hydrogen and methylthio.

In the above structures,  $R^3$  is selected from hydrogen, alkoxy, aryloxy, alkyl and aryl. Preferred  $R^3$  is selected from hydrogen, about  $C_1$ - $C_4$  alkoxy and phenoxy. Most preferred are hydrogen, methoxy and ethoxy.

In Formula (A), X is selected from -O- and -S- and R<sup>9</sup> is selected from C<sub>1</sub>-C<sub>10</sub> alkyl, aryl and heteroaryl. Preferred XR<sup>9</sup> moieties are selected from alkoxy and alkylthio having from about 1 to about 10 carbon atoms, phenoxy and phenylthio. More preferred XR<sup>9</sup> moieties are selected from methoxy, ethoxy, methylthio, ethylthio, phenoxy and phenylthio, all unsubstituted.

With respect to compounds defined in sub-part (A) of Formula (I), where the compounds include only two fused rings as the compound's nucleus, preferred compounds made according to the present process are those listed in Table I.

Table I

A	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	R <sup>5</sup>	R <sup>6</sup>	$\mathbb{R}^7$
N	$\overline{A}$	Н	OMe	Н	F	F
COMe	$\overline{A}$	Н	ОМе	Н	F	F

СМе	1	Н	ОМе	Н	F	F
CCI	<u> </u>	Н	OMe	Н	F	F
CF		Н	ОМе	Н	F	F
СН		Н	ОМе	Н	F	F
COCF3		H	ОМе	H	F	F
COCHF2		Н	OMe	Н	F	F
N	Å.F	Н	OMe	H <sub>.</sub>	F	F
COMe	F	Н	OMe	Н	F	F
СМе	<b></b>	Н	OMe	Н	F	F
CCI		Н	OMe	Н	F	F
CF	<b></b>	Н	OMe	Н	F	F
СН	F	Н	ОМе	H	F	F
COCF3	F	Н	ОМе	Н	F	F
COCHF2	<u></u>	Н	OMe	Н	F	F
N	Et	Н	ОМе	Н	F	F
COMe	Et	Н	ОМе	Н	F	F
СМе	Et	H	OMe	Н	F	F
CCI	Et	Н	ОМе	Н	F	F
CF	Et	Н	ОМе	Н	F	F
CH	Et	Н	ОМе	Н	F	F
COCF3	Et	Н	OMe	Н	F	F
COCHF2	Et	Н	ОМе	Н	F	F
N	t-But	Н	ОМе	Н	F	F

CCI	t-But	Н	OMe	Н	F	F
CF	t-But	н	OMe	H	F	F.
CH	t-But	H	OMe	H	F	F
	t-Dut			Н	F	F
N		Н	OMe			
СОМе	¢"	H	ОМе	Н	F	F
СМе	<b>\rightarrow</b>	Н	OMe	Н	F	F
CCI	+	Н	ОМе	H	F	F
CF	+	Н	ОМе	H	F	F
СН	<b>\</b>	Н	OMe	Н	F	F
COCF3		H	OMe	Н	F	F
COCHF2		Н	ОМе	Н	F	F
N	7	SMe	ОМе	Н	F	F
СОМе	7	SMe	OMe	Н	F	F
СМе	7	SMe	OMe	Н	F	F
CCI	7	SMe	OMe	H	F	F

CF	$\bot$	SMe	OMe	Н	F	F
CH	7	SMe	OMe	Н	F	F
COCF3	7	SMe	OMe	Н	F	F
COCHF2	7	SMe	OMe	H	F	F
N	Et	SMe	OEt	H	F	F
СОМе	Et	SMe	OEt	Н	F	F
СМе	Et	SMe	OEt	H	F	F
CCI	Et	SMe	OEt	H	F	F
CF	Et	SMe	OEt	H	F	F
CH	Et	SMe	OEt	H	F	F
COCF3	Et	SMe	OEt	Н	F	F
COCHF2	Et	SMe	OEt	Н	F	F
N	t-But	SMe	OEt	H	F	F
СМе	t-But	SMe	OEt	H	F	F
CCI	t-But	SMe	OEt	H	F	F
CF	t-But	SMe	OEt	H	F	F
CH	t-But	SMe	OEt	H	F	F
COCF3	t-But	SMe	OEt	H	F	F
COCHF2	t-But	SMe	OEt	H	F	F
N		SMe	OEt	Н	F	F
СОМе	¢	SMe	OEt	Н	F	F
СМе	¢*	SMe	OEt	H	F	F

		·				
CCI		SMe	OEt	Н	F	F
CF		SMe	OEt	Н	F	F
СН	<b>\</b>	SMe	OEt	Н	F	F
COCF3	<b>\</b>	SMe	OEt	Н	F	F
COCHF2		SMe	OEt	н	F	<b>. F</b>
N	$\overline{A}$	Н	OMe	NH2	F	F
COMe	<u> </u>	H	OMe	NH2	F	F
СМе	4	Н	OMe	NH2	F	F
CCI	$\overline{A}$	Н	OMe	NH2	F	F
CF	<u> </u>	H	OMe	NH2	F	F
CH	7	H	OMe	NH2	F.	F
COCF3	<u>\</u>	H	OMe	NH2	F	F
COCHF2	7	H	OMe	NH2	F	F
N		Н	OMe	NH2	F	F
COMe	<b>△</b> F	Н	OMe	NH2	F	F
СМе	<u></u>	H	OMe	NH2	F	F

CCI		Н	ОМе	NH2	F	F
CF	<u></u>	Н	OMe	NH2	F	F
СН	<u></u>	Н	OMe	NH2	F	F
COCF3		Н	ОМе	NH2	F	F
COCHF2	1	Н	ОМе	NH2	F	F
N	Et	Н	OMe	NH2	·F	F
СОМе	Et	H	OMe	NH2	F	F
СМе	Et	Н	OMe	NH2	F	F
CCI	Et	H	OMe	NH2	F	F
CF	Et	H	OMe	NH2	F	F
СН	Et	H	OMe	NH2	F	F
COCF3	Et	Н	OMe	NH2	F	F
COCHF2	Et	H	OMe	NH2	F	F
СМе	t-But	Н	OMe	NH2	F	F
CCI	t-But	H	OMe	NH2	F	F
CF	t-But	H	OMe	NH2	F	F
CH	t-But	Н	ОМе	NH2	F	F
N	<b>\</b>	H	OMe	NH2	F	F
СОМе	¢,	Н	ОМе	NH2	F	F
СМе	<b>\</b>	Н	ОМе	NH2	F	F
CCI ·	+	Н	ОМе	NH2	F	F

<del></del> -	<del>- , - , - , -</del> ,		016	NH2	F	F
CF		Н	OMe	·	·	
CH		Н	OMe	NH2	F	F
COCF3	<b>\</b>	н.	OMe	NH2	F	F
COCHF2	<b>\</b>	Н	OMe	NH2	F	F
N	$\overline{A}$	H	OMe	Me	F	F
COMe	$\overline{A}$	Н	OMe	Ме	F	F
СМе	$\overline{A}$	Н	ОМе	Ме	F	F
CCI	$\overline{A}$	Н	ОМе	Me	F	F
CF	$\Delta$	Н	OMe	Me	F	F
CH	$\perp$	Н	OMe	Me	F	F
COCF3	$\overline{A}$	H	OMe	Me	F	F .
COCHF2	<u> </u>	Н	ОМе	Me	F	F
N	F	Н	ОМе	Ме	F	F
COMe	F	Н	OMe	Me	F	F
СМе	∆.	H	OMe	Me	F	F
CCI		H	OMe	Me	F	F
CF	<b></b>	H .	OMe	Me	F	F

CIT -	<del></del>		<del></del>			
СН		H	OMe	Me	F	F
COCF3		Н	OMe	Me	F	F
COCHF2	<u></u>	Н	OMe	Me	F	F
N	Et	Н	OMe	Me	F	F
COMe	Et	Н	OMe	Me	F	F
СМе	Et	Н	OMe	Me	F	F
CCI	Et	Н	OMe	Me	F	F
CF	Et	Н	OMe	Me	F	F
СН	Et	Н	OMe	Me	F	F
COCF3	Et	Н	OMe	Me	F	F
COCHF2	Et	Н	OMe	Me	F	F
N	t-But	Н	OMe	Me	F	F
СМе	t-But	Н	OMe	Me	F	F
CCI	t-But	Н	OMe	Me	F	F
CF	t-But	Н	OMe	Me	F	F
СН	t-But	Н	OMe	Me	F	F
N		Н	OMe	Ме	F	F
СОМе	+	Н	ОМе	Me	F	F
СМе		Н	OMe	Ме	F	F
CCI		Н	ОМе	Ме	F	F
CF	<b>\</b>	Н	OMe	Me	F	F

CITY T		Н	OMe	Me	F	F
CH						
COCF3	4	Н	OMe	Ме	F	F
COCHF2		н	OMe	Me	F	F
N	$\overline{A}$	SMe	OEt	Н	Н	F
СОМе	7	SMe	OEt	Н	H	F
СМе	$\overline{A}$	SMe	OEt	Н	H	F
CCI	7	SMe	OEt	Н	H	F
CF	<u>\</u>	SMe	OEt	Н	Н	F
СН	人	SMe	OEt	H	H	F
COCF3	7	SMe	OEt	Н	H	F
COCHF2	7	SMe	OEt	Н	H	F
N		SMe	OEt	Н	Н	F
COMe	<u></u>	SMe	OEt	H	Н	F
СМе	→ Å,	SMe	OEt	Н	Н	F
CCI	F	SMe	OEt	H	H	F
CF	F	SMe	OEt	Н	H	F
СН		SMe	OEt	Н	H	F
COCF3		SMe	OEt 24	Н	l n	

COCTITO	<del></del>		<del></del>			
COCHF2		SMe	OEt	H	H	F
N	Et	SMe	OEt	H	Н	F
COMe	Et	SMe	OEt	H	Н	F
СМе	Et	SMe	OEt	H	Н	F
CCI	Et	SMe	OEt	H	Н	F
CF	Et	SMe	OEt	Н	H	F
CH	Et	SMe	OEt	Н	H	F
COCF3	Et	SMe	OEt	H	H	F
COCHF2	Et	SMe	OEt	Н	H	F
N	t-But	SMe	OEt	H	Н	F
СМе	t-But	SMe	OEt	H	H	F
CCI	t-But	SMe	OEt	Н	H	F
CF	t-But	SMe	OEt	Н	H	F
СН	t-But	SMe	OEt	Н	H	F
N	<b>\rightarrow</b>	SMe	OEt	Н	H	F
СОМе	+	SMe	OEt	Н	H	F
СМе	+	SMe	OEt	Н	H	F
CCI		SMe	OEt	Н	Н	F
CF		SMe	OEt	Н	н	F
СН	+	SMe	OEt	H	Н	F

			T		Н	F
COCF3		SMe	OEt	Н	n	
COCHF2	<b>\</b>	SMe	OEt ·	Н	Н	F
N		Н	OMe	NH2	Н	F
COMe	$\overline{\lambda}$	Н	OMe	NH2	Н	F
СМе	$\overline{\lambda}$	Н	OMe	NH2	Н	F
CCI	$\overline{A}$	Н	OMe	NH2	Н	F
CF	<u>\</u>	Н	OMe	NH2	H	F
СН	7	Н	OMe	NH2	Н	F
COCF3	7	Н	OMe	NH2	H	F
COCHF2	7	Н	OMe	NH2	Н	F
N	F	Н	OMe	NH2	H	F
COMe	Å.F	Н	OMe	NH2	Н	F
СМе	P	Н	OMe	NH2	H	F
CCI	<b>Å</b> F	Н	OMe	NH2	Н	F
CF	Å.F	Н	OMe	NH2	H	F
СН		Н	OMe	NH2	Н	F
COCF3	<u></u>	Н	OMe	NH2	Н	F
COCHF2	F	Н	OMe	NH2	Н	F

					_	:
N	Et	Н	OMe	NH2	Н	F
СОМе	Et	H	OMe	NH2	H	F
СМе	Et	H	OMe	NH2	H	F
CCI	Et	Н	OMe	NH2	Н	F
CF	Et	Н	OMe	NH2	Н	F
СН	Et	Н	OMe	NH2	Н	F
COCF3	Et	H	OMe	NH2	Н	F
COCHF2	Et	H	OMe	NH2	Н	F
СМе	t-But	Н	OMe	NH2	Н	F
CC1	t-But	Н	OMe	NH2	Н	F
CF	t-But	H	OMe	NH2	Н	F
СН	t-But	Н	OMe	NH2	Н	· F
N	¢,	Н	ОМе	NH2	Н	F
СОМе	<b>\</b>	Н	ОМе	NH2	Н	F
СМе	<b>\</b>	Н	OMe	NH2	Н	F
CCI	¢	Н	ОМе	NH2	Н	F
CF	<b>\</b>	Н	ОМе	NH2	Н	F
СН	<b>\</b>	Н	OMe	NH2	Н	F
COCF3	<b>†</b>	Н	OMe	NH2	Н	F

	<del></del>	н	OMe	NH2	Н	F
COCHF2		n	·			
N	7	Н	OMe	Ме	Н	F
COMe	7	Н	OMe	Me	Н	F
СМе		Н	OMe	Me	Н	F
CCI	$\overline{A}$	Н	OMe	Me	Н	F
CF	$\overline{A}$	Н	ОМе	Ме	Н	F
СН	$\overline{A}$	Н	OMe	Me	Н	F
COCF3	<u>\lambda</u>	Н	OMe	Ме	Н	F
COCHF2	$\overline{\lambda}$	Н	OMe	Me	Н	F
N	F	Н	OMe	Ме	Н	F
СОМе	Å.P	Н	OMe	Ме	H	F
CMe	<u></u>	H	OMe	Ме	H	F
CCI	Å.ª	Н	OMe	Ме	H	F
CF		Н	OMe	Me	Н	F
CH	F	H	OMe	Me	Н	
COCF3	∆*	H	OMe	Me	H	F
COCHF2	∆.º	Н	OMe	Me	Н	F
N	Et	Н	OMe	Me	H	F
COMe	Et	Н	OMe	Me	H	F
СМе	Et	Н	OMe	Me	Н	F

CCI ER H OME ME H F  CF ER H OME ME H F  CH ER H OME ME H F  COCF3 ER H OME ME H F  COCHF2 ER H OME ME H F  N H OME ME H F  COME H OME ME H F  COME H OME ME H F  CCI H OME ME H F  CCOCF3 H OME ME H F  CCOCF3 H OME ME H F  CCOCF4 H OME ME H F  CCOCHF2 H OME ME H F  CCOCHF2 H OME ME H F  CCOCHE  H OME H CI F  CCME  H OME H CI F	001	T ===		<del></del>	γ — — — — — — — — — — — — — — — — — — —		
CH Et H OMe Me H F  COCF3 Et H OMe Me H F  COCHF2 Et H OMe Me H F  N H OMe Me H F  COMe H F  COMe H F  COME H OME ME H F  COCF3 H OME ME H F  COCF3 H OME ME H F  COCF4 H OME ME H F  COCF5 H OME ME H F  COCHF2 H OME ME H F  COCHF2 H OME ME H F  COME A H OME ME H F	CCI	Et	H	OMe	Me	H	F
COCF3         Et         H         OMe         Me         H         F           COCHF2         Et         H         OMe         Me         H         F           N         H         OMe         Me         H         F           COMe         H         OMe         Me         H         F           CMe         H         OMe         Me         H         F           CCI         H         OMe         Me         H         F           CCI         H         OMe         Me         H         F           CCH         H         OMe         Me         H         F           COCF3         H         OMe         Me         H         F           COCHF2         H         OMe         H         CI         F           COMe         H         OMe         H         CI         F		Et	H	OMe	Me	Н	F
COCHF2 Et H OMe Me H F  N	<u> </u>	Et	H	OMe	Me	H	F
N         ↓         H         OMe         Me         H         F           COMe         ↓         H         OMe         Me         H         F           CMe         ↓         H         OMe         Me         H         F           CCI         ↓         H         OMe         Me         H         F           CF         ↓         H         OMe         Me         H         F           CH         ↓         H         OMe         Me         H         F           COCF3         ↓         H         OMe         Me         H         F           COCHF2         ↓         H         OMe         H         CI         F           COMe         ↓         H         OMe         H         CI         F	<b></b>	Et	Н	OMe	Me	H	F
COMe	COCHF2	Et	H	OMe	Me	H	F
CMe		+	H	ОМе	Ме	Н	F
CCI				OMe	Ме	H	F
CF H OMe Me H F  CH H OMe Me H F  COCF3 H OMe Me H F  COCHF2 H OMe Me H F  COMe A H OME H CI F  COMe A H OME H CI F		<b>\</b>	Н	OMe	Ме	H	F
CH H OMe Me H F  COCF3 H OMe Me H F  COCHF2 H OMe Me H F  N H OMe H CI F  COMe H OME H CI F	·	<b>\rightarrow</b>	Н	OMe	Ме	H	F
COCF3 H OMe Me H F  COCHF2 H OMe Me H F  N		+	H	ОМе	Ме	H	F
COCHF2 H OMe Me H F  N		+	Н	ОМе	Ме	H	F
N H OMe H Cl F  COMe			Н	OMe	Ме	Н	F
COMe			H	ОМе	Me	Н	F
Δ					Н	Cl	F
CMe H OMe H Cl F					Н	Cl	F
	СМе	$\Delta$	Н	ОМе	Н	Cl	F

	<del></del>	TT	0)46	Н	CI	F
CC1		Н	OMe	n		
CF	$\overline{A}$	Н	OMe	H	Cl	F
СН	$\overline{A}$	Н	OMe	Н	Cl	F
COCF3	$\overline{A}$	Н	OMe	H	Cl	F
COCHF2	$\overline{A}$	Н	OMe	Н	Cl	F
N		Н	ОМе	Н	Cl	F
СОМе	<b></b>	Н	OMe	Н	Cl	F
СМе	<u>ا</u>	Н	ОМе	Н	Cl	F
CCl	<u></u>	Н	ОМе	H	Cl	F
CF		H	OMe	Н	Cl	F
CH		Н	OMe	Н	Cl	F
COCF3	<b></b>	Н	OMe	Н	Cl	F
COCHF2		Н	OMe	H	Cl	F
N	Et	· H	OMe	Н	Cl	F
COMe	Et	Н	OMe	Н	Cl	F
СМе	Et	Н	OMe	Н	Cl	F
CCI	Et	Н	OMe	H	Cl	F
CF	Et	Н	OMe	Н	CI	F
СН	Et	Н	OMe	Н	Cl	F
COCF3	Et	Н	OMe	H	CI	F
COCHF2	Et	Н	OMe	Н	Cl	F
· N	t-But	Н	OMe	Н	Cl	F
COMe	t-But	Н	OMe	Н	Cl	F
СМе	t-But	н	OMe	. н	Cl	F

CCI	t-But	Н	OMe	Н	CI	F
CF	t-But	. H	OMe	Н	Cl	F
СН	t-But	Н	OMe	Н	CI	F
COCF3	t-But	Н	OMe	Н	Cl	·
COCHF2	t-But	Н	OMe	н	Cl	F
N		Н	OMe	H	CI	F
	<b>P</b>		ONIC		a	F
СОМе		H	ОМе	H	Cl	F
СМе	<b>\</b>	Н	ОМе	Н	Cl	F.
CCI		Н	OMe	Н	. Cl	F
CF	<b>\</b>	Н	OMe	Н	Cl	F
СН	¢,	Н	OMe	Н	CI	F
COCF3	¢	Н	ОМе	Н	CI	F
COCHF2		Н	ОМе	Н	Cl	F
N	A	SMe	ОМе	H.	Cl	F
СОМе		SMe	ОМе	Н	Cl	F
СМе		SMe	OMe_	Н	Cl	F

			- T	<b>u</b> · 1	Ci	F
CCI	_ \_	SMe	OMe	H		
CF	7	SMe	OMe	Н	Cl	F
CH		SMe	OMe	Н	Cl	F
COCF3		SMe	OMe	Н	Cl	F
COCHF2	$\overline{\lambda}$	SMe	ОМе	Н	CI	F
N	Et	SMe	OMe	Н	Cl	F
COMe	Et	SMe	OMe	H	Cl	F
СМе	Et	SMe	OMe	Н	Cl	F
CCl	Et	SMe	OMe	H	Cl	F
CF	Et	SMe	OMe	H	a	F
СН	Et	SMe	OMe	H	Cl	F
COCF3	Et	SMe	OMe	H	Cl ·	F
COCHF2	Et	SMe	OMe	Н	Cl	F
N		SMe	OEt	H	Cl	F
СОМе	<u></u>	SMe	OEt	Н	Cl	F
СМе		SMe	OEt	Н	Cl	F
CCI		`SMe	OEt	Н	CI	F
CF	Å.P	SMe	OEt	Н	CI	F
CH		SMe	OEt	H	Cl	F
COCF3	P	SMe	OEt	Н	Cl	F
COCHF2	<u></u>	SMe	· OEt	. Н	Cl	F
СМе	t-But	SMe	OEt	Н	Cl	F
CCI	t-But	SMe	OEt	H	Cl	F
CF	t-But	SMe	OEt	Н	CI	F

CH	t-But	SMe	OEt	Н	Cl	F
N		SMe	OEt			
14		SMe	OE	Н	CI	<b>F</b> '
СОМе	<b>\rightarrow</b>	SMe	OEt	H	CI	F
СМе	<b>\</b>	SMe	OEt	Н	CI	F
CCI		SMe	OEt	Н	Cl	F
CF	1	SMe	OEt	Н	Cl	F
СН	<b>\</b>	SMe	OEt	Н	CI	F
COCF3	<b>\</b>	SMe	OEt	Н	Cl	F
COCHF2	<b>\</b>	SMe	OEt	Н	Cl	F
N	$\Delta$	Н	ОМе	NH2	Cl	F
СОМе	$\overline{A}$	Н	ОМе	NH2	Cl	F
СМе	$\overline{A}$	Н	ОМе	NH2	CI	F
CCI	$\overline{A}$	Н	ОМе	NH2	Cl	F
CF	7	H	OMe	NH2	Cl	F
CH	$\triangle$	Н	ОМе	NH2	Cl	F.

		<del></del> -		- 1770 T		
COCF3		H	OMe	NH2	Cl	F
COCHF2	Y	Н	OMe	NH2	Cl	F
N		Н	OMe	NH2	Cl	F
СОМе		Н	ОМе	NH2	CI	F
СМе		Н	ОМе	NH2	Cl	F
CCI		Н	OMe	NH2	Cl	F
CF	<u></u>	H	OMe	NH2	Cl	F
CH		Н	ОМе	NH2	Cl	F
COCF3		Н	OMe	NH2	Cl	F
COCHF2		н	OMe	NH2	Cl	F
N	Et	Н	OMe	NH2	Cl	F
СОМе	Et	Н	OMe	NH2	Cl	F
СМе	Et	Н	OMe	NH2	a	F
CCI	Et	Н	OMe	NH2	C1	F
CF ·	Et	Н	OMe	NH2	Cl	F
СН	Et	Н	OMe	NH2	Cl	F
COCF3	Et	Н	OMe	NH2	Cl	F
COCHF2	Et	H	OMe	NH2	Cl	F
N	t-But	Н	OMe	NH2	Cl	F
CMe	t-But	Н	ОМе	NH2	a	F
CCI	t-But	Н	OMe	NH2	Cl	F
CF	t-But	Н	OMe	NH2	CI	F
CH	t-But	Н	OMe	NH2	Cl	F
N	+	H	OMe	NH2	Cl	F

						i
СОМе	<b>\rightarrow</b>	Н	ОМе	NH2	CI	F
СМе	4	Н	OMe	NH2	Cl	F
CCI	+	H	ОМе	NH2	Cl	F
CF	+	Н	ОМе	NH2	Cl	<b>.</b>
СН	<b>\</b>	Н	OMe	NH2	Cl	F
COCF3	<b>\</b>	Н	OMe	NH2	Cl	F
COCHF2	<b>\</b>	H	ОМе	NH2	Cl	F
N	7	Н	ОМе	Me	Cl	F
СОМе	7	Н	ОМе	Me	Cl	F
СМе	A	Н	ОМе	Ме	CI	F
CCI	$\forall$	Н	ОМе	Ме	Cl	F
CF	$\bot$	Н	ОМе	Me	Cl	F
CH	$\Delta$	Н	ОМе	Me	Cl	F
COCF3	7	H	ОМе	Ме	CI	F
COCHF2	7	Н	ОМе	Ме	a	F

N		H	OMe	Me	Cl	F
COMe		Н	OMe	Me	Cl	F
СМе	<u></u>	Н	OMe	Me	Cl	F
CCI	Å₽.	H	OMe	Me	CI	F
CF		Н	ОМе	Me	Cl	F
СН	F	Н	OMe	Me	CI	F
COCF3	<b></b>	Н	OMe	Me	Cl	F
COCHF2	P	H	OMe	Me	Cl	F
. N	Et	Н	OMe	Me	Cl	F
COMe	Et	Н	OMe	Me	Cl	F
СМе	Et	Н	OMe	Me	Cl	F
CCI	Et	H	OMe	Me	CI	F
CF	Et	Н	OMe	Me	Cl	F
СН	Et	H	OMe	Me	Cl	F
COCF3	Et	H.	OMe	Me	CI	F
COCHF2	Et	H	OMe	Me	Cl	. <b>F</b>
N	t-But	Н	OMe	Me	Cl	F
CMe	t-But	Н	OMe	Me	Cl	F
CCI	t-But	H	OMe	Me	Cl	F
CF	t-But	н	OMe	Me	CI	F
CH	t-But	Н	OMe	Me	Cl	F
N	<b>\</b>	H	OMe	Ме	Cl	F
СОМе	4	Н	OMe	Ме	Cl	F

СМе	+	Н	ОМе	Ме	Cl	F
CCI	+	Н	ОМе	Ме	Cl	F
CF	†	H	ОМе	Ме	CI	F
СН	<b>\</b>	Н	ОМе	Ме	Cl	F
COCF3	Image: Control of the	Н	ОМе	Ме	CI	F
COCHF2	+	H	OMe	Ме	CI	F
N	$\overline{A}$	Н	ОМе	Н	F	Br
СОМе	$\overline{A}$	H	ОМе	Н	F	Br
СМе	$\Delta$	Н	ОМе	Н	F	Br
CCl		Н	ОМе	Н	F	Br
CF	$\overline{A}$	Н	ОМе	H	F	Br
СН	4	Н	ОМе	Н	F	Br
COCF3	$\overline{A}$	Н	ОМе	H	F	Br
COCHF2	4	Н	ОМе	Н	F	Br
N		Н	OMe	H	F	Br

	<del></del>					
COMe		Н	OMe	Н	F	Br
CMe	Å.	Н	OMe	Н	F	Br
CCI	Å₽	Н	OMe	Н	F	Br
CF		н	ОМе	Н	F	Br
СН		Н	ОМе	Н	F	Br
COCF3	<u></u>	Н	ОМе	H	F	Br
COCHF2		Н	ОМе	Н	F	Br
N	Et	Н	OMe	Н	F	Br
COMe	Et	Н	OMe	H	F	Br
СМе	Et	Н	OMe	Н	F	Br
CCI	Et	H	ОМе	Н	F	Br
CF	Et	H	OMe	H	F	Br
CH	Et	H	ОМе	Н	F	Br
COCF3	Et	H	OMe	Н	F	Br
COCHF2	Et	H	OMe	Н	F	Br
N	t-But	Н	OMe	Н	F	Br
СМе	t-But	H	OMe	Н	F	Br
CCI	t-But	Н	OMe	Н	F	Br
CF	t-But	H	OMe	H	F	Br
CH	t-But	Н	OMe	H	F	Br
N	<b>\</b>	H	ОМе	Н	F	Br
COMe	<b>\</b>	Н	OMe	Н	F	Br
СМе	<b>\rightarrow</b>	Н	ОМе	Н	F	Br

	<del></del>		<u> </u>		·	i
. CCI		H	ОМе	H	F	Br
CF	4	Н	OMe	Н	F	Br
СН	<b>\\</b>	Н	OMe	H	F	Br
COCF3	4	Н	ОМе	Н	F	Br
COCHF2	<b>\</b>	Н	OMe	Н	F	Br
N	-	SMe	ОМе	Н	F	Br
N	<u> </u>	SMe	OEt	Н	F	Br
СОМе	7	SMe	OEt	Н	F	Br
СМе	$\overline{A}$	SMe	OEt	Н	F	Br
CCI	$\overline{A}$	SMe	OEt	Н	F	Br
CF	$\Delta$	SMe	OEt	Н	F	Br
СН	4	SMe	OEt	Н	F	Br
COCF3		SMe	OEt	H	F	Br
COCHF2	$\Delta$	SMe	OEt	Н	F	Br
N .		SMe	OEt	Н	F	Br

СОМе	T	SMe	OEt	Н	F	Br
СМе		SMe	OEt	H	F	Br
CCI		SMe	OEt	Н	F	Br
CF	<u></u>	SMe	OEt .	Н	F	Br
СН		SMe	OEt	Н	F	Br
COCF3	٨.	SMe	OEt	Н	F	Br
COCHF2		SMe	OEt	Н	F	Br
N	Et	SMe	OEt	Н	F	Br
COMe	Et	SMe	OEt	H	F	Br
СМе	Et	SMe	OEt	H	F	Br
CCI	Et	SMe	OEt	H	F	Br
CF	Et	SMe	OEt	Н	F	Br
СН	Et	SMe	OEt	Н	F	Br
COCF3	Et	SMe	OEt	H	F	Br
COCHF2	Et	SMe	OEt	. H	F	Br
N	t-But	SMe	OEt	H	F	Br
СМе	t-But	SMe	OEt	H	F	Br
CCI	t-But	SMe	OEt	H	F	Br
CF	t-But	SMe	OEt	H	F	Br
СН	t-But	SMe	OEt	Н	F	Br
N	<b>\</b>	SMe	OEt	H	F	Br
СОМе	4	SMe	OEt	Н	F	Br
СМе	+	SMe	OEt ,	Н	F	Br

CO!		T	<del></del>			
CCI		SMe	OEt	H	F	Br
CF	+	SMe	OEt	Н	F	Br
CH	¢	SMe	OEt	Н	F	Br
COCF3	<b>\</b>	SMe	OEt	H	F	Br
COCHF2	Image: Control of the	SMe	OEt	н	F	Br
N	4	H	ОМе	NH2	F	Br
СОМе	7	Н	ОМе	NH2	F	Br
СМе	7	Н	ОМе	NH2	. F	Br
CCI	<u>\</u>	Н	OMe	NH2	F	Br
CF	A	Н	ОМе	NH2	F	Br
СН	$\overline{A}$	Н	ОМе	NH2	F	Br
COCF3	$\overline{A}$	Н.	ОМе	NH2	F	Вг
COCHF2	$\Delta$	Н	ОМе	NH2	F	Br
N		H	ОМе	NH2	F	Br
СОМе	Å.F	Н	ОМе	NH2	F	Br
СМе		Н	ОМе	NH2	F	Br

	·					
CCI	F	H	OMe	NH2	F	Br
CF	۵.	Н	ОМе	NH2	F	Br
СН	Å₽	Н	ОМе	NH2	F	Br
COCF3	<u></u>	Н	ОМе	NH2	F	Br
COCHF2	<b></b>	Н	OMe	NH2	F	Br
N	Et	Н	OMe	NH2	F	Br
COMe	Et	Н	OMe	NH2	F	Br
СМе	Et	Н	OMe	NH2	F	Br
CC1	Et	Н	OMe	NH2	F	Br
CF	Et	Н	OMe	NH2	F	Br
СН	Et	Н	OMe	NH2	F	Br
COCF3	Et	Н	OMe	NH2	F	Br
COCHF2	Et	Н	OMe	NH2	F	Br
N	t-But	Н	OMe	NH2	F	Br
COMe	t-But .	Н	OMe	NH2	F	Br
СМе	t-But	Н	OMe	NH2	F	Br
CCI	t-But	H	OMe	NH2	F	Br
CF	t-But	Н	OMe	NH2	F	Br
CH	t-But	H	OMe	NH2	F	Br
COCF3	t-But	H	OMe	NH2	F	Br
COCHF2	t-But	H	OMe	NH2	F	Br
N	<b>\rightarrow</b>	Н	ОМе	NH2	F	Br
СОМе	<b>\rightarrow</b>	H	ОМе	NH2	F	Br
СМе	<b>\rightarrow</b>	H	ОМе	NH2	F	Br

CCI	<del>†                                    </del>	7	T	<del></del>	<del></del>	<u> </u>
CCI	<b>P</b>	Н	ОМе	NH2	F	Br
CF	+	Н	ОМе	NH2	F	Br
СН	+	Н	ОМе	NH2	F	Br
COCF3	4	Н	ОМе	NH2	F	Вт
COCHF2	<b>\rightarrow</b>	Н	ОМе	NH2	F	Br
N	$\overline{A}$	Н	ОМе	Me	F	Br
СОМе	$\overline{A}$	Н	ОМе	Me	F	Br
СМе	$\overline{A}$	Н	ОМе	Ме	F	Br
CCI	$\Delta$	Н	ОМе	Me	F	Br
CF	$\overline{A}$	Н	ОМе	Ме	F	Br
СН	7	Н	ОМе	Ме	F	Br
COCF3	$\overline{A}$	Н	ОМе	Me	F	Br
COCHF2	7	Н	ОМе	Me	F	Br
N	<u></u> ↓	Н	ОМе	Me	F	Br
СОМе		Н	ОМе	Me	F	Br
СМе		Н	ОМе	Me	F	Br

CCI		H	OMe	Me	F	Br
CCI						
CF	<u> </u>	Н	OMe	Ме	F	Br
CH	Å.F	Н	OMe	Ме	F	Br
COCF3		Н	ОМе	Ме	F	Br
COCHF2	<b></b>	Н	ОМе	Ме	F	Br
N	Et	Н	ОМе	Me	F	Br
COMe	Et	Н	ОМе	Me	F	Br
СМе	Et	H	OMe	Me	F	Br
CCI	Et	H	OMe	Me	F	Br
CF	Et	Н	OMe	Me	F	Br
CH	Et	H	ОМе	Me	F	Br
COCF3	Et	H	OMe	Me	F	Br
COCHF2	Et	H	OMe	Me	F	Br
N	t-But	H	OMe	Me	F	Br
СМе	t-But	H	OMe	Me	F	Br
CCI	t-But	H	OMe	Me	F	Br
CF	t-But	H	OMe	Me	F	Br
CH	t-But	Н	OMe	Me	F	Br
N	<b>\</b>	Н .	ОМе	Me	F	Br
COMe	<b>\</b>	Н	ОМе	Me	F	Br
СМе	<b>\rightarrow</b>	Н	OMe	Me	F	Br
CCI	¢	Н	OMe	Me	F	Br

CF		Н	ОМе	Me	F	Br
		<b></b>	OMC	Wic	r	
СН	<b>\</b>	H	ОМе	Me	F	Br
COCF3	<b>\</b>	H	ОМе	Me	F	Br
COCHF2	<b>\</b>	Н	ОМе	Me	F	Br
N	$\overline{A}$	SMe	OEt	H	Н	Br
СОМе	$\overline{A}$	SMe	OEt	Н	H	Br
СМе	7	SMe	OEt	H	H	Br
CCI	$\overline{A}$	SMe	OEt	H	Н	Br
CF	$\overline{A}$	SMe	OEt	H	Н	Br
СН	$\overline{A}$	SMe	OEt	H	H	Br
COCF3	7	SMe	OEt	H	Н	Br
COCHF2	7	SMe	OEt	Н	Н	Br
N	<b></b>	SMe	OEt	Н	H	Br
СОМе	F	SMe	OEt	H	н	Br
СМе		SMe	OEt	Н	Н	Br
CCI	Å.F	SMe:	OEt	H	H	Br
CF		SMe	OEt	Н	Н	Br

				T		
CH		SMe	OEt	Н	н	Br
COCF3		SMe	OEt	Н	Н	Br
COCHF2	<u></u>	SMe	OEt	H	Н	Br
N	Et	SMe	OEt	Н	H	Br
СОМе	Et	SMe	OEt	H	H	Br
СМе	Et	SMe	OEt	H	H	Br
CCI	Et	SMe	OEt	H	H	Br
CF	Et	SMe	OEt	H	Н	Br
CH	Et	SMe	OEt	Н	Н	Br
COCF3	Et	SMe	OEt	Н	Н	Br
COCHF2	Et	SMe	OEt	H	H	Br
N	t-But	SMe	OEt	Н	H	Br
СМе	t-But	SMe	OEt	H	H	Br
CCI	t-But	SMe	OEt	Н	H	Br
CF	t-But	SMe	OEt	Н	Н	Br
CH	t-But	SMe	OEt	Н	H	Br
N	4	SMe	OEt	Н	H	Br
COMe	<b>\</b>	SMe	OEt	Н	Н	Br
СМе	4	SMe	OEt	Н	H	Br
CCI	<b>\</b>	SMe	OEt	H	H	Br
CF	¢"	SMe	OEt	Н	Н	Br

	<del></del>					
СН		SMe	OEt	Н	Н	Br
COCF3	4	SMe	OEt	H	Н	Br
COCHF2	+	SMe	OEt	Н	Н	Br
N	\ \d	Н	ОМе	NH2	Н	Br
СОМе	4	Н	ОМе	NH2	H	Br
СМе	7	Н	ОМе	NH2	Н	Br
CCI	7	Н	OMe	NH2	Н	Br
CF	7	Н	ОМе	NH2	Н	Br
CH	7	H	OMe	NH2	Н	Br
COCF3	7	Н	ОМе	NH2	Н	Br
COCHF2	7	Н	ОМе	NH2	H	Br
N		Н	OMe	NH2	Н	Br
СОМе		H	ОМе	NH2	Н	Br
СМе	J.	Н	ОМе	NH2	H	Br
CCI	F	Н	OMe	NH2	H	Br
CF	F	Н	ОМе	NH2	Н	Br
CH	F	H	OMe	NH2	H	Br
COCF3		H	OMe	NH2	H	Br

N Et H OMe NH2 H  COMe Et H OMe NH2 H  CMe Et H OMe NH2 H  CCI Et H OMe NH2 H  CCI Et H OMe NH2 H  CCF Et H OMe NH2 H  CCH Et H OMe NH2 H  COCF3 Et H OMe NH2 H  COCHF2 Et H OMe NH2 H  N t-But H OMe NH2 H  COMe t-But H OMe NH2 H  CCI t-But H OMe NH2 H  CCI t-But H OMe NH2 H  CCI t-But H OMe NH2 H  CCH t-But H OMe NH2 H  COCF3 t-But H OMe NH2 H  COCF3 t-But H OMe NH2 H  COCF3 t-But H OMe NH2 H  COCF4 t-But H OMe NH2 H  COCHF2 t-But H OME NH2 H  COCHF2 t-But H OME NH2 H  COME H OME NH2 H  COME H OME NH2 H  COME H OME NH2 H	Br	a.	н	NIU2 T	0)4-	77		
COMe				NAZ	OMe	H		COCHF2
CMe	Br	Ð	Н	NH2	OMe	Н	Et	N
CCI Et H OMe NH2 H  CF Et H OMe NH2 H  CH Et H OMe NH2 H  COCF3 Et H OMe NH2 H  COCHF2 Et H OMe NH2 H  N t-But H OMe NH2 H  COMe t-But H OMe NH2 H  CCI t-But H OMe NH2 H  CCI t-But H OMe NH2 H  CF t-But H OMe NH2 H  COCF3 t-But H OMe NH2 H  COCHF2 t-But H OMe NH2 H  COCHF2 t-But H OME NH2 H  COCHF3 t-But H OME NH2 H  COCHF4 t-But H OME NH2 H  COCHF5 t-But H OME NH2 H  COCHF6 t-But H OME NH2 H  COCHF6 t-But H OME NH2 H  COCHF7 t-But H OME NH2 H  COCHF7 t-But H OME NH2 H  COCHF8 t-But H OME NH2 H  COCHF9 t-But H OME NH2 H  COCHF9 t-But H OME NH2 H  COME THE OME THE	Br	18	H	NH2	OMe	H	Et	COMe
CF Et H OMe NH2 H  CH Et H OMe NH2 H  COCF3 Et H OMe NH2 H  COCHF2 Et H OMe NH2 H  N t-But H OMe NH2 H  COMe t-But H OMe NH2 H  CMe t-But H OMe NH2 H  CCI t-But H OMe NH2 H  CCH t-But H OMe NH2 H  COCF3 t-But H OMe NH2 H  COCF3 t-But H OMe NH2 H  COCCF3 t-But H OMe NH2 H  COCCHF2 t-But H OMe NH2 H  COCCHF2 t-But H OMe NH2 H  COME H OME NH2 H	Br	E	Н	NH2	OMe	H	Et	СМе
CH Et H OMe NH2 H  COCF3 Et H OMe NH2 H  COCHF2 Et H OMe NH2 H  N t-But H OMe NH2 H  COMe t-But H OMe NH2 H  CMe t-But H OMe NH2 H  CCI t-But H OMe NH2 H  CF t-But H OMe NH2 H  CH t-But H OMe NH2 H  COCF3 t-But H OMe NH2 H  COCHF2 t-But H OMe NH2 H  COME H OME NH2 H	Br	F	Н	NH2	OMe	Н	Et	CCI
COCF3 Et H OMe NH2 H  COCHF2 Et H OMe NH2 H  N t-But H OMe NH2 H  COMe t-But H OMe NH2 H  CMe t-But H OMe NH2 H  CCI t-But H OMe NH2 H  CCI t-But H OMe NH2 H  CCI t-But H OMe NH2 H  CCH t-But H OMe NH2 H  COCF3 t-But H OMe NH2 H  COCHF2 t-But H OMe NH2 H  COCME H OME NH2 H  COME NH2 H	Br	F	H	NH2	OMe	Н	Et	CF
COCHF2 Et H OMe NH2 H  N t-But H OMe NH2 H  COMe t-But H OMe NH2 H  CMe t-But H OMe NH2 H  CCI t-But H OMe NH2 H  CF t-But H OMe NH2 H  CH t-But H OMe NH2 H  COCF3 t-But H OMe NH2 H  COCHF2 t-But H OMe NH2 H  COCHF2 t-But H OMe NH2 H  COME H OME NH2 H	Br	F	H	NH2	OMe	Н	Et	CH
N t-But H OMe NH2 H  COMe t-But H OMe NH2 H  CMe t-But H OMe NH2 H  CCI t-But H OMe NH2 H  CF t-But H OMe NH2 H  CH t-But H OMe NH2 H  COCF3 t-But H OMe NH2 H  COCHF2 t-But H OMe NH2 H  N H OMe NH2 H  COMe NH2 H	Br	F	H	NH2	OMe	Н	Et	COCF3
COMe t-But H OMe NH2 H  CMe t-But H OMe NH2 H  CCI t-But H OMe NH2 H  CF t-But H OMe NH2 H  CH t-But H OMe NH2 H  COCF3 t-But H OMe NH2 H  COCHF2 t-But H OMe NH2 H  N	Br	I	H	NH2	OMe	Н	Et	COCHF2
CMe t-But H OMe NH2 H  CCI t-But H OMe NH2 H  CF t-But H OMe NH2 H  CH t-But H OMe NH2 H  COCF3 t-But H OMe NH2 H  COCHF2 t-But H OMe NH2 H  N	Br	I	H	NH2	OMe	Н	t-But	N
CCI t-But H OMe NH2 H  CF t-But H OMe NH2 H  CH t-But H OMe NH2 H  COCF3 t-But H OMe NH2 H  COCHF2 t-But H OMe NH2 H  N	Br	1	Н	NH2	OMe	Н	t-But	COMe
CF t-But H OMe NH2 H  CH t-But H OMe NH2 H  COCF3 t-But H OMe NH2 H  COCHF2 t-But H OMe NH2 H  N H OMe NH2 H  COMe NH2 H  COMe H OME NH2 H  COMe H OME NH2 H  COMe H OME NH2 H	Br	1	Н	NH2	OMe	Н	t-But	СМе
CH t-But H OMe NH2 H  COCF3 t-But H OMe NH2 H  COCHF2 t-But H OMe NH2 H  N	Br	1	Н	NH2	OMe	Н	t-But	CCI
COCF3 t-But H OMe NH2 H  COCHF2 t-But H OMe NH2 H  N	Br		H	NH2	OMe	Н	t-But	CF
COCHF2 t-But H OMe NH2 H  N	Br		H	NH2	OMe	Н	t-But	CH
N H OMe NH2 H  COMe H OMe NH2 H  CMe H OMe NH2 H  CCI H OME NH2 H	Br		H	NH2	OMe	Н	t-But	COCF3
COMe H OMe NH2 H  CMe H OMe NH2 H  CCI H OME NH2 H	Br		H	NH2	OMe	Н	t-But	COCHF2
CMe H OMe NH2 H  CCI H OMe NH2 H	Br	1	Н	NH2	OMe	Н		N
CMe H OMe NH2 H  CCI H OMe NH2 H				·				
CCI H OMe NH2 H	Br		H	NH2	OMe	H		COMe
CCI H OMe NH2 H	-	.					Y	
	Br		H	NH2	OMe	H		СМе
							4	
	Br		Н	NH2	OMe	Н		CCI
	·							
CF H OMe NH2 H	Вт		Н	NH2	OMe	H		CF

СН		Н	ОМе	NH2	H	Br
COCF3	4	Н	ОМе	NH2	Н	Br
COCHF2	4	H	ОМе	NH2	Н	Br
N	<u> </u>	H	ОМе	Ме	Н	Br
СОМе	4	Н	ОМе	Me	Н	Br
СМе	7	H	OMe	Me	Н	Br
cci	7	H	ОМе	Me	Н	Br
CF	4	Н	OMe	Ме	Н	Br
СН	7	Н	ОМе	Me	Н	Br
COCF3	Ţ	Н	ОМе	Ме	H	Br
COCHF2	7	Н	ОМе	Ме	Н	Br
N		Н	ОМе	Ме	Н	Br
СОМе		Н	ОМе	Ме	H	Br
СМе	٨.	Н	ОМе	Ме	H	Br
CCI		Н	ОМе	Me	Н	Br
CF	<u></u>	Н	ОМе	Ме	Н	Br
СН		Н	ОМе	Me	H	Br
COCF3		Н	ОМе	Me	H	Br

		<del> </del>				
COCHF2		H	OMe	Me	Н	Br
N	Et	Н	OMe	Me	Н	Br
COMe	Et	H	OMe	Me	Н	Br
СМе	Et	Н	OMe	Ме	Н	Br
CCl	Et	H	OMe	Me	Н	Br
CF	Et	Н	OMe	Me	Н	Br
CH	Et	H	OMe	Me	Н	Br
COCF3	Et	Н	OMe	Me	Н	Br
COCHF2	Et	H	OMe	Me	н	Br
N	t-But	Н	OMe	Me	H	Br
СМе	t-But	H.	OMe	Me	H	Br
CCI	t-But	Н	OMe	Me	Н	Br
CF	t-But	Н	ОМе	Me	H	. Br
CH	t-But	Н	OMe	Me	Н	Br
N	+	Н	ОМе	Ме	Н	Br
СОМе	+	Н	ОМе	Me	Н	Вт
СМе	d'	Н	ОМе	Me	Н	Br
CCI	<b>\rightarrow</b>	Н	ОМе	Ме	H	Br
CF	<b>\</b>	Н	OMe	Ме	Н	Br
СН	<b>\rightarrow</b>	H	OMe	Me	H	Br

COCF3	7'	7.7	0)(	T-57	T	<u>_</u>
	<b>P</b>	H	ОМе	Me	H	Br
COCHF2		Н	ОМе	Me	Н	Br ;
N	Y	Н	ОМе	Н	CI	Br
СОМе	$\overline{A}$	Н	OMe	Н	Cl	Br
СМе	<u> </u>	Н	OMe	H	a	Br
CCI	$\overline{A}$	Н	OMe	Н	Cl	Br
CF	$\perp$	Н	ОМе	Н	CI	Br
СН	_ \_	Н	OMe	Н	Cl	Br
COCF3		Н	OMe	H	Cl	Br
COCHF2	$\Delta$	Н	OMe	Н	CI	Br
N	<u></u>	Н	ОМе	Н	CI	Br
COMe		Н	OMe	Н	CI	Br
CMe		Н	ОМе	H	Cl	Br
CCI		H	ОМе	H	Cl	Br
CF		Н	OMe	H	Cl	Br
СН		H	ОМе	H	Cl	Br
COCITE		Н	OMe	H	CI	Br
COCHF2		H	ОМе	Н	Cl	Br

N	Et	Н	OMe	Н	Cl	Br
COMe	Et	Н	OMe	Н	Cl	Br
CMe	Et	Н	OMe	H	Cl	Br
CCI	Et	Н	OMe	Н	Cl	Br
CF	Et	Н	OMe	H	Cl	Br
CH	Et	Н	OMe	н	Cl	Br
COCF3	Et	Н	OMe	Н	Cl	Br
COCHF2	Et	H	ОМе	Н	Cl	Br
N	t-But	Н	OMe	Н	Cl	Br
СМе	t-But	Н	OMe	H	Cl	Br
CCI	t-But	H	OMe	Н	Cl .	Br
CF	t-But	Н	OMe	Н	Cl	Br
СН	t-But	H	OMe	Н	Cl	Br
N	<b>\</b>	Н	OMe	Н	Cl	Br
СОМе	<b>\</b>	H	OMe	Н	CI	Br
СМе	<b>\rightarrow</b>	Н	ОМе	H	Cl	Br
CCI	¢.	Н	ОМе	Н	CI	Br
CF	¢.	Н	ОМе	Н	Cl	Br
СН	¢,	H .	OMe	Н	Cl	Br
COCF3	<b>\rightarrow</b>	H	OMe	Н	Cl	Br

COCTTO	<del></del>	T	<del></del>		T	
COCHF2		H	ОМе	H	а	Br
N	<u> </u>	SMe	ОМе	Н	a	Br ;
COMè	7	SMe	ОМе	Н	a	Br
СМе	7	SMe	ОМе	Н	а	Br
CC1		SMe	ОМе	Н	а	Br
CF		SMe	ОМе	Н	CI	Br
СН	$\Delta$	SMe	ОМе	H	CI	Br
COCF3		SMe	ОМе	H	Cl	Br
COCHF2		SMe	ОМе	Н	Cl	Br
N		SMe	ОМе	Н	Cl	Br
COMe		SMe	ОМе	H	Cl	Br
CMe CCl		SMe	OMe	H	Cl	Br
CF		SMe	OMe	Н	Cl	Br
		SMe	ОМе	H	CI	Br
СН		SMe	ОМе	H	Cl	Br
COCF3		SMe	ОМе	Н	Cl	Br
COCHF2	<b></b>	SMe	OMe	Н	Cl	Br
CF		SMe	OEt	Н	Cl	Br
СН		SMe	OEt	Н	a	Br

COCF3		SMe	OEt	H	Cl	Br
COCHF2		SMe	OEt	Н	Cl	Br
N	Et	SMe	OEt	Н	Cl	Br
COMe	Et	SMe	OEt	Н	Cl	Br
СМе	Et	SMe	OEt	H	Cl	Br
CC1	Et	SMe	OEt	Н	Cl	Br
CF	Et	SMe	OEt	H	Cl	Вт
CH	Et	SMe	OEt	H	Cl	Br
COCF3	Et	SMe	OEt	H	Cl	Вг
COCHF2	Et	SMe	OEt	H	CI	Br
N	t-But	SMe	OEt	Н	Cl	Br
СМе	t-But	SMe	OEt	н	Cl	Br
CCI	t-But	SMe	OEt	H	CI .	Br
СМе	Et	Н	OMe	H	F	NO2
CCI	Et	Н	OMe	Н	F	NO2
CF	Et	H	OMe	Н	F	NO2
СН	Et	H	OMe	Н	F	NO2
COCF3	Et	Н	OMe	H	F	NO2
COCHF2	Et	Н	OMe	Н	F	NO2
N	t-But	Н	OMe	Н	F	NO2
СМе	t-But	H	OMe	Н	F	NO2
CC1	t-But	Н	OMe	H	F	NO2
CF	t-But	Н	OMe	Н	F	NO2
CH	t-But	Н	OMe	Н	F	NO2
N	↓ ·	Н	ОМе	Н	F	NO2
COMe	4	Н	OMe	Н	F	NO2

СМе		Н	OMe	Н	F	NO2
	Y					ł
CCI		H	OMe	H	F	NO2
	1 Y	· ·			· .	
CF		H	ОМе	H	F	NO2
	Ť					
СН		H	ОМе	Н	F	NO2
COCF3		H	ОМе	H	F	NO2
	<b>)</b>					
COCHF2		H	OMe	H.	. , <b>F</b>	NO2
	7					
N	<u>\</u>	SMe	OEt	H	F	NO2
СОМе	$\overline{\lambda}$	SMe	OEt	Н	F	NO2
СМе	$\overline{A}$	SMe	OEt	Н	F	NO2
CCI	7	SMe	OEt	H	F	NO2
CF	$\overline{A}$	SMe	OEt	Н	F	NO2
СН	7	SMe	OEt	Н	F	NO2
COCF3	$\overline{A}$	SMe	OEt	H	F	NO2
COCHF2	7	SMe	OEt	Н	F	NO2
N		SMe	OEt	Н	F	NO2

	<del></del>	0) (	OF4	н	F	NO2
COMe		SMe	OEt	п	r	NOZ
СМе	Å.	SMe	OEt	H	F	NO2
CCI		SMe	OEt	Н	F	NO2
CF	٨.	SMe	OEt	H	F	NO2
СН	P	SMe	OEt	Н	F	NO2
COCF3		SMe	OEt	Н	F	NO2
COCHF2	₹	SMe	OEt	Н	F	NO2
N	Et	SMe	OEt	H	F	NO2
COMe	Et	SMe	OEt	Н	F	NO2
СМе	Et	SMe	OEt	Н	F	NO2
CCI	Et	SMe	OEt	H	, F	NO2
CF	Et	SMe	OEt	Н	F	NO2
CH	Et	SMe	OEt	H	F	NO2
COCF3	Et	SMe	OEt	H	F	NO2
COCHF2	Et	SMe	OEt	H	F	NO2
N	t-But	SMe	OEt	Н	F	NO2
СМе	t-But	SMe	OEt	H	F	NO2
CCI	t-But	SMe	OEt	H	F	NO2
CF	t-But	SMe	OEt	H	F	NO2
CH	t-But	SMe	OEt	H	F	NO2
N	4	SMe	OEt	Н	F	NO2
COMe	4	SMe	OEt	H	F	NO2
СМе	+	SMe	OEt	Н.	F	NO2

CCI		SMe	OEt	Н	F	NO2
CF	+	SMe	OEt	Н	F	NO2
СН	+	SMe	OEt	Н	F	NO2
COCF3		SMe	OEt	Н	F	NO2
COCHF2		SMe	. OEt	Н	F	NO2
N	7	Н	OMe	NH2	F	NO2
СОМе	<u> </u>	Н	OMe	NH2	F	NO2
СМе	7	Н	OMe	NH2	F	NO2
CCI	7	Н	OMe	NH2	F	NO2
CF	7	Н	OMe	NH2	F	NO2
СН	7	Н	ОМе	NH2	F	NO2
COCF3	$\overline{A}$	Н	OMe	NH2	F	NO2
COCHF2	7	Н	OMe	NH2	F	NO2
N		Н	OMe	NH2	F	NO2
СОМе		Н	OMe	NH2	F	NO2
СМе		Н	ОМе	NH2	F	NO2

						·
CCl		Н	OMe	NH2	F	NO2
CF		Н	OMe	NH2	F	NO2
CH		Н	OMe	NH2	F	NO2
COCF3		H	ОМе	NH2	F	NO2
COCHF2	<b></b>	Н	OMe	NH2	F	NO2
N	Et	Н	OMe	NH2	F	NO2
COMe	Et	H	OMe	NH2	F	NO2
СМе	Et	Н	OMe	NH2	F	NO2
CCI	Et	Н	OMe	NH2	F	NO2
CF	Et	H	OMe	NH2	F	NO2
CH	Et	Н	OMe	NH2	F	NO2
COCF3	Et	Н	OMe	NH2	F	NO2
COCHF2	Et	Н	OMe	NH2	F	NO2
N	t-But	Н	OMe	NH2	F	NO2
СМе	t-But	H.	OMe	NH2	F	NO2
CCI	t-But	Н	OMe	NH2	F	NO2
CF	t-But	Н	OMe	NH2	F	NO2
CH	t-But	Н	OMe	NH2	F	NO2
N	¢.	Н	ОМе	NH2	F	NO2
COMe	¢	Н	OMe	NH2	F	NO2
СМе	¢'	H	OMe	NH2	F	NO2
CCl	4	Н	OMe	NH2	F	NO2

					<del></del>	
CF		H	OMe	NH2	F	NO2
CH	<b>\</b>	Н	ОМе	NH2	F	NO2
COCF3		H	OMe	NH2	F	NO2
COCHF2	<b>\</b>	Н	ОМе	NH2	F	NO2
N	7	Н	OMe	Me	F	NO2
COMe	7	Н	OMe	Ме	F	NO2
СМе	$\overline{A}$	Н	ОМе	Ме	F	NO2
CCI	$\bot$	Н	OMe	Me	F	NO2
CF	$\overline{A}$	Н	ОМе	Me	F	NO2
СН	$\overline{A}$	Н	ОМе	Me	F	NO2
COCF3	$\overline{A}$	H	ОМе	Ме	F	NO2
COCHF2	$\overline{A}$	Н	OMe	Me	F	NO2
N		H	OMe	Ме	F	NO2
СОМе		Н	OMe	Ме	F	NO2
СМе	<u> </u>	Н	ОМе	Me	F	NO2
CCI		H	ОМе	Me	F	NO2
CF	<u></u>	<b>H</b> .	ОМе	Me	F	NO2

CH		Н	OMe	Me	F	NO2
COCF3		Н	OMe	Me	F	NO2
COCHF2		Н	OMe	Me	F	NO2
N	Et	Н	OMe	Me	F	NO2
COMe	Et	Н	OMe	Me	F	NO2
СМе	Et	Н	OMe	Me	F	NO2
CCl	Et	Н	OMe	Me	F	NO2
CF	Et	Н	OMe	Me	F	NO2
СН	Et	H	OMe	Me	F	NO2
COCF3	Et	H	OMe	Me	F	NO2
COCHF2	Et	Н	OMe	Me	F	NO2
N.	t-But	Н	OMe	Me	F	NO2
СМе	t-But	H	OMe	Me	F	NO2
CCI	t-But	H	OMe	Me	F	NO2
CF	t-But	Н	OMe	Me	F	NO2
CH	t-But	Н	OMe	Me	F	NO2
N	<b>\</b>	Н	ОМе	Me	F	NO2
СОМе	<b>\</b>	н	ОМе	Ме	F	NO2
СМе	+	Н	OMe	Me	F	NO2
CCI	<b>\</b>	Н	ОМе	Me	F	NO2
CF	¢,	Н	OMe	Ме	F	NO2

СН	+	Н	ОМе	Ме	F	NO2
COCF3		Н	ОМе	Ме	F	NO2
COCHF2	<b>\</b>	Н	ОМе	Ме	F	NO2
N	· L	SMe	OEt	Н	Н	NO2
СОМе	$\overline{A}$	SMe	OEt	H	Н	NO2
СМе	7	SMe	OEt	Н	Н	NO2
CCI	$\overline{A}$	SMe	OEt	Н	Н	NO2
CF	7	SMe	OEt .	Н	Н	NO2
СН	7	SMe	OEt	Н	Н	NO2
COCF3	7	SMe	OEt	Н	Н	NO2
COCHF2	7	SMe	OEt	Н	Н	NO2
N	<b></b>	SMe	OEt	Н	Н	NO2
COMe		SMe	OEt	H	H	NO2
СМе		SMe	OEt	Н	H	NO2
CCI		SMe	OEt	H	H	NO2
CF	<b>Å</b> ₽	SMe	OEt	Н	H	NO2
СН		SMe	OEt	H	H	NO2
COCF3		SMe	OEt	H	Н	NO2

COCHF2		SMe	OEt	Н	Н	NO2
N	Et	SMe	OEt	Н	Н	NO2
COMe	Et	SMe	OEt	H	н	NO2
СМе	Et	SMe	OEt	Н	Н	NO2
CCI	Et	SMe	OEt	H	Н	NO2
CF	Et	SMe	OEt	H	H	NO2
CH	Et	SMe	OEt	H	Н	NO2
COCF3	Et	SMe	OEt	Н	H	NO2
COCHF2	Et	SMe	OEt	Н	H	NO2
N	t-But	SMe	OEt	Н	H	NO2
СМе	t-But	SMe	OEt	Н	Н	NO2
CCI	t-But	SMe	OEt	Н	Н	NO2
CF	t-But	SMe	OEt	H	Н	NO2
СН	t-But	SMe	OEt	H	Н	NO2
N	\ \	SMe	OEt	Н	Н	NO2
СОМе	4	SMe	OEt	н	н	NO2
СМе	Image: Control of the	SMe	OEt	Н	Н	NO2
CCI	4	SMe	OEt	Н	H	NO2
CF	+	SMe	OEt	Н	Н	NO2
CH	<b>\rightarrow</b>	SMe	OEt	Н	Н	NO2

COCF3	<del></del>	SMe	OEt	Н	Н	NO2
coars		01120	<b>V</b>			
COCHF2	<b>\</b>	SMe	OEt	H	Н	NO2
N	$\overline{A}$	Н	OMe	NH2	Н	NO2
СОМе	7	H	OMe	NH2	Н	NO2
СМе	7	H	OMe	NH2	Н	NO2
CCI	7	Н	OMe	NH2	Н	NO2
CF	$\overline{A}$	Н	OMe	NH2	Н	NO2
СН	. 👃	H	OMe	NH2	Н	NO2
COCF3	$\overline{A}$	Н	OMe	NH2	Н	NO2
COCHF2	$\overline{A}$	H	OMe	NH2	Н	NO2
N	Å.	H	ОМе	NH2	Н	NO2
COMe		H	ОМе	NH2	Н	NO2
СМе	<u></u>	H	OMe	NH2	H	NO2
CCI	<u></u>	H	OMe	NH2	H	NO2
CF		Н	OMe	NH2	H	NO2
CH		Н	OMe	NH2	H	NO2
COCF3		Н	ОМе	NH2	Н	NO2
COCHF2		H	OMe	NH2	H	NO2

Et Et Et Et Et Et Et Et Et t-But t-But t-But	H H H H H H H H H H	OMe	NH2	H H H H H H H H H H H H H	NO2 NO2 NO2 NO2 NO2 NO2 NO2 NO2 NO2 NO2
Et Et Et Et Et -But t-But t-But	H H H H H H H H	OMe	NH2	H H H H H H H H H	NO2 NO2 NO2 NO2 NO2 NO2 NO2 NO2 NO2 NO2
Et Et Et Et Et -But t-But t-But	H H H H H H H	OMe	NH2	H H H H H H H	NO2 NO2 NO2 NO2 NO2 NO2 NO2 NO2 NO2
Et Et Et Et Et L-But L-But L-But L-But	H H H H H H H	OMe	NH2	H H H H H H H	NO2 NO2 NO2 NO2 NO2 NO2 NO2 NO2
Et Et Et Et t-But t-But t-But t-But	H H H H H H	OMe	NH2	H H H H H H	NO2 NO2 NO2 NO2 NO2 NO2 NO2 NO2
Et Et Et t-But t-But t-But t-But	H H H H H	OMe OMe OMe OMe OMe OMe OMe OMe	NH2 NH2 NH2 NH2 NH2 NH2 NH2 NH2 NH2	H H H H H	NO2 NO2 NO2 NO2 NO2 NO2 NO2
Et Et t-But t-But t-But t-But	H H H H H	OMe OMe OMe OMe OMe OMe OMe	NH2 NH2 NH2 NH2 NH2 NH2 NH2 NH2 NH2	H H H H	NO2 NO2 NO2 NO2 NO2 NO2
Et t-But t-But t-But t-But	H H H H	OMe OMe OMe OMe OMe OMe	NH2 NH2 NH2 NH2 NH2 NH2	H H H H	NO2 NO2 NO2 NO2 NO2
t-But t-But t-But	н н н н	OMe OMe OMe	NH2 NH2 NH2 NH2	н н н н	NO2 NO2 NO2 NO2
t-But t-But t-But	H H H	OMe OMe OMe	NH2 NH2 NH2	н н н	NO2 NO2 NO2
t-But t-But	H	OMe OMe	NH2 NH2	H	NO2 NO2
t-But	Н	ОМе	NH2	Н	NO2
					· .
	Н	ОМе	NH2	H	NO2
				ł	1
		1			
1	H	OMe	NH2	Н	NO2
Q					
1,	H	OMe	NH2	Н	NO2
Ÿ.					
<u> </u>	Н	OMe	NH2	н	NO2
Q .					
1 ,	H	OMe	NH2	H	NO2
Q .					
	H	OMe	NH2	H	NO2
T	H	OMe	NH2	Н	NO2
<del>\\</del> -\\\\		. 1			ŀ
-					

COCHF2	ΙΙ.	H	OMe	NH2	H	NO2
						:
		ļ				
N	1	H	OMe	Me	H	NO2
	Δ					
COMe		H	ОМе	Me	H	NO2
CMo		77	OM	76		
СМе	· 👃	H	OMe	Me	H	NO2
CCI	<u> </u>	Н	OMe	Me	Н	NO2
	Δ					
CF	<u></u>	Н	OMe	Me	Н	NO2
	Δ					•
СН	<u></u>	Н	ОМе	Me	H	NO2
	Δ		<del>- 2. 2 -</del>			
COCF3		H	OMe	Me	H	NO2
COCHF2	1	н	ОМе	Me	H	NO2
	Δ	<del></del>	51.15		••	NOL
N	1.	Н	OMe	Me	H	NO2
СОМе		H	OMe	Me	H	NO2
СМе		H	OMe	Me	Н,	NO2
Civic		**	ONIC	ivie	Π,	NOZ
CCI		H	OMe	Me	H	NO2
		77	0).6		<del> </del>	
CF		H	ОМе	Me	H	NO2
СН	<u> </u>	Н	ОМе	Me	H	NO2
·						
COCF3		H	ОМе	Me	H	NO2
COCHF2	<del></del>	н	OMe	Me	H	NO2
· ·		- <del>-</del> -	<del></del>			
N.	Et	Н.	OMe	Me	H	NO2
COMe	Et	Н	OMe	Me	H	NO2
CMe	Et	Н	OMe	Me	Н	NO2
		,		<u> </u>		

				_		
CCI	Et	Н	ОМе	Me	Н	NO2
CF	Et	Н	OMe	Me	H	NO2
СН	Et	H	OMe	Me	Н	NO2
COCF3	Et	H	OMe	Me	H	NO2
COCHF2	Et	Н	ОМе	Me	Н	NO2
N	t-But	Н	ОМе	Me	Н	NO2
СМе	t-But	H	OMe	Me	Н	NO2
CCI	t-But	Н	OMe	Me	Н	NO2
CF	t-But	Н	OMe	Me	H	NO2
СН	t-But	H	OMe	Me	H	NO2
N		Н	ОМе	Ме	Н	NO2
СОМе	<b>\</b>	Н	OMe	Me	Н	NO2
СМе	+	Н	ОМе	Me	Н	NO2
CCI	+	Н	OMe	Ме	Н	NO2
CF	¢.	H	OMe	Ме	Н	NO2
CH	Ů,	Н	OMe	Ме	Н	NO2
COCF3	d'	Н	OMe	Ме	Н	NO2
COCHF2	<b>\</b>	Н	OMe	Me	Н	NO2

N ·	_ \_	H	OMe	Н	Cl	NO2
COMe	$\overline{A}$	Н	OMe	H	Cl	NO2
СМе	$\overline{A}$	Н	OMe	Н	Cl	NO2
CCI	$\overline{A}$	Н	OMe	Н	Cl	NO2
CF	$\overline{A}$	Н	OMe	Н	Cl	NO2
СН	$\overline{A}$	Н	OMe	Н	CI	NO2
COCF3		Н	OMe	Н	Cl	NO2
COCHF2	$\overline{A}$	Н	OMe	Н	Cl	NO2
N	<u>\</u>	Н	OMe	Н	а	NO2
СОМе		Н	ОМе	H	Cl	NO2
СМе		Н	OMe	H	а	NO2
CCI	₹	H	OMe	H	a	NO2
CF		H	OMe	H	CI	NO2
CH		Н	OMe	H	Cl	NO2
COCF3		Н	OMe	H	Cl	NO2
COCHF2		Н	OMe	Н	CI	NO2
N	Et ·	H	OMe	Н	Cl	NO2
COMe	Et	Н	OMe	H	Cl	NO2
СМе	Et	Н	OMe	H	CI	NO2
CCI	Et	H	OMe	H	Cl	NO2
CF	Et	H	OMe	Н	CI	NO2
CH	Et	H	OMe	Н	Cl	NO2

COCF3	Et	н	OMe	Н	Cl	NO2
COCHF2	Et	Н	OMe	Н	Cl	NO2
N N	t-But	н	OMe	Н	Cl	NO2
	t-But	Н	OMe	H	Cl	NO2
COMe	t-But	H	OMe	н	Cl	NO2
CMe	t-But	Н	OMe	н	Cl	NO2
CC1 CF	t-But	H	OMe	H	Cl	NO2
	t-But	H	OMe	H	Cl	NO2
CH	t-But	H	OMe	H	Cl	NO2
COCF3	t-But	H	OMe	H	Cl	NO2
COCHF2	t-But		OMe	H	Cl	NO2
N		н	OMe			1,02
2016	-	H	OMe	H	Cl	NO2
СОМе		n	OWIC	**		
СМе	<b>\</b>	Н	OMe	Н	CI	NO2
CCI	, r	H	OMe	Н	Cl	NO2
	Q					
CF		Н	ОМе	Н	Cl	NO2
СН		H	OMe	Н	Cl	NO2
COCF3	→	Н	OMe	H	CI	NO2
COCHF2	¢.	н	OMe	Н	Cl	NO2

WO 02/48113 PCT/US01/48536

Ņ	1	SMe	OEt	Н	CI	NO2
СОМе	7	SMe	OEt	н	Cl	NO2
СМе	7	SMe	OEt	н	CI	NO2
CCI	7	SMe	OEt	H	CI	NO2
CF	7	SMe	OEt	Н	CI	NO2
CH	$\overline{A}$	SMe	OEt	Н	Cl	NO2
COCF3	$\overline{A}$	SMe	OEt	H	а	NO2
COCHF2	$\overline{A}$	SMe	OEt	Н	CI	NO2
N		SMe	OEt	H	Cl	NO2
СОМе	<u>\</u>	SMe	OEt	H	а	NO2
СМе		SMe	OEt	Н	Cl	NO2
CCI	<b></b>	SMe	OEt	H	Cl	NO2
CF	<u></u>	SMe	OEt	Н	Cl	NO2
CH		SMe	OEt	H	a	NO2
COCF3		SMe	OEt	Н	a	NO2
COCHF2	<b></b>	SMe	OEt	H	CI	NO2
N	Et	SMe	OEt	Н	Cl	NO2
COMe	Et	SMe	OEt	H	Cl ·	NO2
CMe	Et	SMe	OEt	H	CI	NO2
CCI	Et	SMe	OEt	H	Cl	NO2
CF	Et	SMe	OEt	Н	CI	NO2
CH	Et	SMe	OEt	Н	Cl	NO2

				77		NO2
COCF3	Et	SMe	OEt	H	Cl	
COCHF2	Et	SMe	OEt	Н	Cl	NO2
N	t-But	SMe	OEt	Н	Cl	NO2
СМе	t-But	SMe	OEt	H	Cl	NO2
CCI	t-But	SMe	OEt	H	CI .	NO2
CF	t-But	SMe	OEt	H	Cl	NO2
CH	t-But	SMe	OEt	H	a	NO2
N	<b>\</b>	SMe	OEt	Н	Cl	NO2
COMe	¢,	SMe	OEt	Н	CI	NO2
СМе	<b>\</b>	SMe	OEt	Н	CI	NO2
CCI	<b>\</b>	SMe	OEt	н	Cl	NO2
CF	<b>\</b>	SMe	OEt	Н	CI	NO2
CH	<b>\rightarrow</b>	SMe	OEt	H	Cl	NO2
COCF3	4	SMe	OEt	Н	Cl	NO2
COCHF2	¢,	SMe	OEt	Н	Cl	NO2
N	7	Н	OMe	NH2	Cl	NO2
COMe	7	H	OMe	NH2	CI	NO2

СМе		Н	OMe	NH2	Cl	NO2
CCI	$\triangle$	Н	OMe	NH2	а	NO2
CF	$\overline{A}$	Н	OMe	NH2	а	NO2
CH	· \	Н	ОМе	NH2	Cl	NO2
COCF3	$\overline{A}$	H	OMe	NH2	Cl	NO2
COCHF2	$\Delta$	H	OMe ·	NH2	Cl	NO2
N	<u></u>	Н	OMe	NH2	Cl	NO2
СОМе		Н	ОМе	NH2	CI	NO2
СМе	٨.	Н	OMe	NH2	CI	NO2
CCI		Н	OMe	NH2	a	NO2
CF		H	OMe	NH2	CI	NO2
СН		Н	OMe	NH2	CI	NO2
COCF3	۵.	Н	OMe	NH2	Cl	NO2
COCHF2	<u></u>	Н	OMe	NH2	Cl	NO2
N	Et	H	OMe	NH2	Cl	NO2
COMe	Et	Н	OMe	NH2	Cl	NO2
СМе	Et	Н	OMe	NH2	Cl	NO2
CCI	Et	Н	OMe	NH2	Cl	NO2
CF	Et	Н	OMe	NH2	Cl	NO2
СН	Et	Н	OMe	NH2	Cl	NO2
COCF3	Et	Н	OMe	NH2	Cl	NO2
COCHF2	Et	H	ОМе	NH2	Cl	NO2
N	t-But	Н	OMe	NH2	Cl	NO2

		H	OMe	NH2	Cl	NO2	
CMe	t-But		OMe	NH2	CI	NO2	
CCI	t-But	Н	OMe	NH2	Cl	NO2	•
CF	t-But	Н		NH2	cı	NO2	
CH	t-But	Н	OMe		CI	NO2	
N		·H	OMe	NH2	4	1102	
			. !		-		
		Н	OMe	NH2	CI	NO2	
COMe		<b>I</b>	020				
1							
СМе	+ 1.	H	OMe	NH2	CI	NO2	
		1					
			0)/	NH2	CI	NO2	
CCI		H	OMe	NFLZ			
	14						
- CTF	<del>-  </del>	H	OMe	NH2	CI	NO2	
CF							
						NO2	-
СН	1	H	OMe	NH2	CI	NOZ	
<u> </u>		H	OMe	NH2	- cı	NO2	1
COCF	3	n.	Olvic				
COCH	F2   1 .	H	OMe	NH2	CI	NO2	ı
000					<b>.</b> .		١
	,					NO2	-
N	J	H	OMe	Me	CI	1,102	
			OMe	Me	CI	NO2	-
COM	fe	Н	Olare				
		н	OMe	Me	C	NO2	
CM							
CC		H	OM	e Me	; C	l NO2	
							<b></b>
l							

	يند ويسويهم		<del>.</del>		<del></del>	
CF		H	OMe	Me	Cl	NO2
CH	7	Н	OMe	Me	Cl	NO2
COCF3	$\overline{A}$	Н	ОМе	Me	Cl	NO2
COCHF2	$\overline{A}$	H	OMe	Me	Cl	NO2
N	<u></u>	Н	ОМе	Me	Cl	NO2
СОМе		Н	ОМе	Ме	Cl	NO2
СМе		Н	ОМе	Ме	Cl	NO2
CCI		H	ОМе	Ме	а	NO2
CF		H	OMe	Ме	Cl	NO2
CH	<u>J</u>	H	ОМе	Me	CI	NO2
COCF3		Н	OMe	Me	Cl	NO2
COCHF2		Н	ОМе	Me	a	NO2
N	Et	Н	OMe	Ме	CI	NO2
СОМе	Et	Н	ОМе	Me	Cl	NO2
СМе	Et	Н	OMe	Me	Cl	NO2
CCI	Et	H	OMe	Me	Cl	NO2
CF	Et	Н	ОМе	Me	a	NO2
CH	Et	Н	ОМе	Me	Cl	NO2
COCF <sub>3</sub>	Et	Н	OMe	Me	CI	NO2
COCHF <sub>2</sub>	Et	Н	ОМе	Me	Cl	NO2
N	t-But	Н	OMe	Me .	Cl	NO2
СМе	t-But	H	OMe	Me	Cl	NO2
CCI	t-But	Н	ОМе	Me	Cl	NO2
CF	t-But	Н	ОМе	Me	CI	NO2

CH	t-But	н	OMe	Me	Cl	NO2
COCF3	t-But	H	OMe	Me	Ci	NO2
COCHF2	t-But	H	OMe	Me	Cl	NO2
N	<b>\\</b>	Н	ОМе	Ме	а	NO2
COMe	<b>\</b>	Н	OMe	Me	Cl	NO2
СМе	<b>\</b>	Н	ОМе	Ме	Cl	NO2
CCI		Н	OMe	Me	CI	NO2
CF	7	Н	ОМе	Ме	CI	NO2
CH	<b>\</b>	Н	OMe	Ме	а	NO2
COCF3	<b>\</b>	Н	ОМе	Me	Cl	NO2
COCHF2	¢.	Н	OMe	Ме	Cl	NO2
N	7	SMe	OEt	H	Ме	NO2
СОМе	7	SMe	OEt	H	Ме	NO2
СМе	7	SMe	OEt	Н	Me	NO2
CCI	7	SMe	OEt	Н	Me	NO2

WO 02/48113 PCT/US01/48536

CF	7	SMe	OEt	Н	Ме	NO2
СН	7	SMe	OEt	Н	Me	NO2
COCF3		SMe	OEt	Н	Me	NO2
COCHF2	<u>\</u>	SMe	OEt	Н	Ме	NO2
N		SMe	OEt	H	Me	NO2
СОМе		SMe	OEt	Н	Me	NO2
СМе		SMe	OEt	Н	Me	NO2
CCI		SMe	OEt	H	Me	NO2
CF		SMe	OEt	Н	Ме	NO2
CH	- J.	SMe	OEt	Н	Me	NO2
COCF3	4	SMe	OEt	Н	Me	NO2
COCHF2	۷-	SMe	OEt	H	Me	NO2
N	Et	SMe	OEt	Н	Me	NO2
COMe	Et	SMe	OEt	Н	Me	NO2
СМе	Et	SMe	OEt	H	Me	NO2
CCI	Et	SMe	OEt	Н	Me	NO2
CF	Et	SMe	OEt	H	Me	NO2
CH	Et	SMe	OEt	H	Me	NO2
COCF3	Et	SMe	OEt	H	Me	NO2
COCHF2	Et	SMe	OEt	H	Me	NO2
N	t-But	SMe	OEt	Н	Me	NO2
CMe	t-But	SMe	OEt	Н	Me	NO2
CCI	t-But	SMe	OEt	H	Me	NO2
CF	t-But	SMe	OEt	Н	Me	NO2

СН	t-But	SMe	OEt	н	Me	NO2
N	1	SMe	OEt	Н	Me .	NO2
COMe	4	SMe	OEt	Н	Ме	NO2
СМе	4	SMe	OEt	Н	Ме	NO2
CCI	<b>\</b>	SMe	OEt	н	Me	NO2
CF	4	SMe	OEt	Н	Me	NO2
CH	4	SMe	OEt	Н	Me	NO2
COCF3	+	SMe	OEt	Н	Ме	NO2
COCHF2	4	SMe	OEt	Н	Me	NO2
N		Н	OMe	NH2	Ме	NO2
COMe		Н	OMe	NH2	Me	NO2
СМе		H	OMe	NH2	Me	NO2
CCI	+ -	H	OMe	NH2	Me	NO2
CF	1 1	H	OMe	NH2	Me	NO2
CH	1	Н	OMe	NH2	Ме	NO2

COCF3	$\overline{A}$	Н	ОМе	NH2	Me	NO2
COCHF2	$\overline{A}$	Н	ОМе	NH2	Me	NO2
N	<b></b>	Н	OMe	NH2	Me	NO2
СОМе		Н	ОМе	NH2	Me	NO2
СМе		H	ОМе	NH2	Me	NO2
CCI		Н	ОМе	NH2	Me	NO2
CF		H	OMe	NH2	Me	NO2
CH		Н	OMe	NH2	Me	NO2
COCF3		Н	OMe	NH2	Me	NO2
COCHF2	<u></u>	Н	ОМе	NH2	Me	NO2
N	Et	Н	ОМе	NH2	Me	NO2
COMe	Et	H	OMe	NH2	Me	NO2
СМе	Et	Н	OMe	NH2	Me	NO2
. CCl	Et	H	OMe	NH2	Me	NO2
CF	Et	H	OMe	NH2	Me	NO2
СН	Et	Н	OMe	NH2	Me	NO2
COCF3	Et	Н	OMe	NH2	Me	NO2
COCHF2	Et	Н	OMe	NH2	Me	NO2
N	t-But	H	OMe	NH2	Me	NO2
СМе	t-But	H	OMe	NH2	Me	NO2
CCI	t-But	H	OMe	NH2	Me	NO2
CF	t-But	Н	OMe	NH2	Me	NO2
СН	t-But	Н	ОМе	NH2	Me	NO2
N	¢.	Н	OMe	NH2	Ме	NO2

		<del></del>				NTOO
СОМе		н	OMe	NH2	Me	NO2
СМе	*	Н	OMe	NH2	Me	NO2
ccı	<b>\</b>	Н	ОМе	NH2	Ме	NO2
CF	4	н	ОМе	NH2	Ме	NO2
СН	<b>\</b>	Н	ОМе	NH2	Ме	NO2
COCF3	+	H	ОМе	NH2	Me	NO2
COCHF2	+	Н	ОМе	NH2	Me	NO2
N	$\overline{\lambda}$	Н	OMe	Ме	Me	NO2
СОМе	$\overline{A}$	Н	ОМе	Me	Me	NO2
СМе	7	н	OMe	Me	Me	NO2
CCI	7	Н	ОМе	Me	Me	NO2
CF	7	Н	OMe	Me	Me	NO2
СН		Н	OMe	Me	Me	NO2
COCF3	1	H	OMe	Me	Me	NO2
COCHF2	7	Н	OMe	Ме	Me	NO2

N		Н	ОМе	Me	Ме	NO2
СОМе	<b></b>	Н	ОМе	Me	Ме	NO2
СМе		H	ОМе	Ме	Ме	NO2
CCI		Н	ОМе	Ме	Ме	NO2
CF	·	Н	ОМе	Me	Me	NO2
ĊH	<u></u>	Н	ОМе	Ме	Me	NO2
COCF3	₹.	Н	ОМе	Ме	Ме	NO2
COCHF2		Н	ОМе	Me	Me	NO2
N	Et	H	ОМе	Me	Me	NO2
COMe	Et	H	OMe	Me	Ме	NO2
СМе	Et	H	ОМе	Me	Me	NO2
CCI	Et	H	ОМе	Me	Me	NO2
CF	Et	H	ОМе	Me	Me	NO2
СН	Et	Н	ОМе	Me	Me	NO2
COCF3	Et	H	ОМе	Me	Me	NO2
COCHF2	Et	H	ОМе	Me	Me	NO2
N	t-But	Н	ОМе	Me	Me	NO2
СМе	t-But	Н	OMe	Me	Me	NO2
CCI	t-But	Н	OMe	Me	Me	NO2
CF	t-But	Н	ОМе	Me	Me	NO2
CH	t-But	Н	OMe	Me	Me	NO2
N	<b>\</b>	Н	ОМе	Ме	Ме	NO2
СОМе	<b>\</b>	Н	OMe	Ме	Me	NO2

		******T	OM <sub>2</sub>	Me	Me	NO2
СМе		H	OMe	IVIE	IVIC	
CCl		Н	OMe	Me	Me	NO2
CF	<b>\</b>	Н	ОМе	Ме	Ме	NO2
СН	¢	Н	OMe	Ме	Ме	NO2
COCF3	<b>\</b>	Н	OMe	Ме	Ме	, NO2
COCHF2	+	Н	OMe	Me	Me	NO2
COMe	$\overline{\lambda}$	Н	OEt	H	Н	
COMe	7	Н	OEt	Н	F	
СОМе	7	Н	OMe	, н	Н	
СОМе	7	Н	OMe	Н	F	
CF	A00~	Н	OEt	H	F	F.
CF	A00~	Н	OEt	Н	Cl	F
CF	Aco	Н	OEt	NH <sub>2</sub>	Н	F
CF	A00~	H	OEt	Me	F	F
CF	AcS	Н	OEt	H	F	F

CF	Acs~	Н	OEt	NH₂	F	F
CF	Acs	Н	OEt	Ме	a	F
CF	Acs	Н	OEt	H	H	F

With regard to Formula (B) compounds,

R<sup>1</sup> and R<sup>2</sup> of Formula (I) join to form ring L, which is a mono- or bicyclic heterocycle comprising N'.

Preferred compounds of Formula (B) made according to the present process are described in Table B.

Table B

					<u> </u>
A <sup>1</sup>	R³	R <sup>5</sup>	R <sup>6</sup>	R <sup>7</sup>	L
СН	OEt	H	F	СІ	\$
СН	OEt	H	CI	F	
Œ	OEt	H	F	Cl	1
CH	OEt	NH <sub>2</sub>	F	F	7
CF	OEt	NH <sub>2</sub>	F	F	1

CH	OEt	Н	F	F	
СН	OEt	H	CI	F	- N-H
CF	OEt	Н	F	F	
СН	OEt	NH₂	F	F	7
CF	OEt	NH2	F	F	
СН	OEt	н	F	F	_ <u>~</u>
CH	OEt	Н	Cl	F	- X
CF	OEt	Н	F	F	7
CH	OEt	NH <sub>2</sub>	F	F	>
CF	OEt	NH <sub>2</sub>	F	F	_N
CH	OEt	н	P	F	
CH	OEt	Н	Cl	F	-1

CF	OEt	Н	F	F	-
CH	OEt	NH <sub>2</sub>	F	F	<del>†</del>
CF	OEt	NH <sub>2</sub>	F	F	<del>†</del>
СН	OEt	Н	F	F	<u></u>
СН	OEt	Н	Cl	F	<del>\</del>
CF	OEt	H	F	F	<del>\</del>
СН	OEt	NH <sub>2</sub>	F	F	<del>+</del>
CF	OEt	NH <sub>2</sub>	F	F	<u></u>

With regard to Formula (C)

 $R^6$  and  $R^7$  of Formula (I) join to form ring Q, which is a 5- or 6-membered carbocyclic or heterocyclic ring.

Preferred compounds of Formula (C) made according to the present process are described in Table C.

Table C

A	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	R <sup>5</sup>	Q
СОМе	Et	н	OEt	Н	, , , , , , , , , , , , , , , , , , ,
СМе	<b>\</b>	Н	OEt	Me	7-Z-I
CCI	$\overline{A}$	H	OEt	Me	
CF	Å.	H	OEt	Н	SI
CH	t-But	Н	OEt	H	
COCF3	Et	Н	OEt	H	Ů,
COCHF2	7	H	OEt	H	X

# III. Process Conditions:

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The above subject invention process step utilizes a silylating agent that is an organosilicon reagent, which is defined above.

In the key process step, the molar ratio of the organosilicon reagent to reactant (i.e., compound of Formula (A)) is preferably from about 0.5:1 to about 12:1, more preferably from about 1:1 to about 4:1. It will be recognized that these process conditions are merely preferred ranges and is it possible to use both lower and higher molar ratios and still benefit from the inventive process.

The subject invention process step is preferably carried out in an aprotic solvent or combination of solvents. Preferred solvents in which the process step is carried out include, but are not limited to, acetonitrile, N-methylpyrrolidinone (NMP), dimethylformide, N,N-dimethylacetamide, toluene, xylene, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, diglyme; more preferred solvents include acetonitrile, toluene and NMP. Mixtures of one or more solvents may be utilized.

WO 02/48113 PCT/US01/48536

The temperature at which the subject process step is carried out is preferably from about -50°C to about 250°C, more preferably from about -10 °C to about 160°C, more preferably still from about 20°C to about 140°C. The pressure at which the subject reaction step is carried is preferably from about 0.5 atm to about 50 atm, more preferably from about 0.8 atm to about 10 atm, more preferably still from about 1 atm to about 2 atm. Also preferred is that the process step be carried out at about ambient temperature and pressure, or at about reflux temperature and ambient pressure. Again, these process conditions are merely representative and should not be interpreted as in anyway limiting the processes claimed below.

### IV. Specific Synthetic Examples

The following are exemplary, but are not meant to be limiting, regarding variations of the subject invention process step.

#### Example 1

Preparation of Ethyl-1-cyclopropyl-1,4-dihydro-8-methoxy-4-oxo-quinoline-3-carboxylate:

Step a: To a solution of 2,3-dimethoxybenzoic acid (20 g) 1 in dichloromethane (100 ml) is added oxally chloride (34.83 g) followed by 2 drops of anhydrous DMF. The mixture is stirred at room temperature for 1 hr, then heated to reflux for 4h. The solvent is removed by evaporation to give 2,3-dimethoxy benzoyl chloride 2.

Step b: Product 2 is dissolved in anhydrous acetonitrile (20 mL) and is introduced to a stirred solution of triethyl amine (38.3 mL) and ethyl dimethylaminoacrylate (17.29 g) in acetonitrile (130 mL). The mixture is stirred at room temperature for 5 minutes, and then heated to reflux until the reaction goes to completion.

Step c: To the reaction mixture product of Step b, cyclopropylamine (19.01 mL) is added at ambient temperature and stirred until the reaction is complete. The solvent is evaporated, and

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the residue is diluted with ethyl acetate, washed with water and brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure to furnish product 4.

Step d: Product 4 is dissolved in anhydrous acetonitrile (150 mL). N,O-bis(trimethylsilyl)acetamide (115 g) is added. The solution is stirred at room temperature for 0.5 h and heated to reflux. Heating is continued until the reaction is complete. The reaction mixture is concentrated to an oily residue, poured into water, extracted with ethyl acetate, and the solvent removed to furnish product 5.

## Example 2

Ethyl-1-cyclopropyl-1,4-dihydro-7,8-dimethoxy-4-oxoquinoline-3-carboxylate <u>10</u> is prepared by a process similar to that of Example 1 from commercially available 2,3,4-trimethoxy benzoic acid <u>6</u>.

#### Example 3

Ethyl-1-cyclopropyl-1,4-dihydro-8-methoxy-7-nitro-4-oxoquinoline-3-carboxylate <u>16</u> is prepared by a process similar to that of Example 1 from 4-nitro-3,4-dimethoxy benzoic acid <u>12</u>. The 4-nitro-3,4-dimethoxy benzoic acid is prepared from <u>11</u> according to literature procedures. (See, e.g., <u>J. Org. Chem.</u> 42, (6) 1068-1070 (1977) and <u>J. Heterocyclic Chemistry</u> 33, 1171 (1996).)

## Example 4

Ethyl-1-ethyl-1,4-dihydro-8-methoxy-8-bromoquinolone carboxylate <u>21</u> is prepared by a process similar to that of Example 1 from 4-bromo-3,4-dimethoxy benzoic acid <u>17</u>. The 4-bromo-2,3-dimethoxy benzoic acid is prepared according to a literature method. (See e.g., <u>J. Org. Chem.</u> 42(6), 1068-70 (1977).)

#### Example 5:

Ethyl-1-cyclopropyl-1,4-dihydro-8-methoxy-7-fluoroquinolone carboxylate <u>27</u> is prepared by a process similar to that of Example 1 from 4-fluoro-3-methoxy-2-methylthio benzoic acid <u>23</u> or 4-fluoro-2,3-dimethoxybenzoic acid <u>62</u>. The starting benzoic acids are prepared from 4-fluoro-3-methoxy benzoic acid <u>22</u> by a procedure similar to that disclosed in the literature. (See, e.g., US Patent No. 5,334, 753, which is incorporated herein by reference.)

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# Example 6

Ethyl-1,4-dihydro-1-(4-fluorophenyl)-8-fluoro-7-piperidinyl-1,4-dihydro-4-oxo-3-quiniline carboxylic acid <u>32</u> is prepared by a process similar to that of Example 1 from 3-fluoro-2-methoxy-4-piperidinyl benzoic acid <u>28</u>. The starting material <u>28</u> is prepared from 2,3,4-trifluorobenzoic acid by sequential displacement of ortho and para fluorine groups with methoxy and piperidinyl groups by a procedure similar to that reported in literature. (See e.g., <u>Tetrahedron Letters</u> <u>37</u> (36) 6439-6442 (1996).)

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## Example 7

Ethyl-1-cyclopropyl-7-isoindoline-5-yl)-8-methoxy-1,4-dihydro-4-oxoquinoline-3-carboxylate 30 is prepared by a process similar to Step d of Example 1 from the corresponding acrylate derivative 29. This acrylate derivative 29 is prepared by methods depicted in the literature. (See e.g., PCT Application No WO 97/29102.)

#### Example 8

Ethyl 2-chloro-3-nitro-5,12-dihydro-5-oxobenzothiazolo[3,2-a]quinoline-6-carboxy-late 33 is prepared by a process similar to Step d of Example 1 from its cyclization precursor 32. 32 is prepared by reacting 2-chlorobenzothiazole 34 with ethyl-2-methoxy-4-chloro-5-nitrobenzoyl acetate 31 in the presence of sodium hydride.

## Examples 9-11

Cyclization precursors <u>37</u>, <u>40</u> and <u>43</u> are prepared by condensing ethyl 2-methoxy-4-chloro-5-fluoro benzoylacetate <u>35</u> with appropriate imino ethers <u>36</u>, <u>39</u> and <u>42</u>, respectively. The cyclization is carried out as described in Example 1 Step d to produce <u>38</u>, <u>41</u> and <u>44</u>, respectively.

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# Example 12

Ethyl 1,4-dihydro-4-oxo-6-nitro-7-chloro-1H-benz[d]imidazolo[2,3-a]quinoline-3-carboxylate <u>50</u> is prepared form cyclization precursor <u>49</u> as described in Step d of Example 1. The cyclization precursor <u>49</u> is prepared form 2-methoxy-4-chloro-5-nitrobenzoic acid <u>45</u> as shown below using similar procedures reported in literature. (See e.g., <u>J. Med. Chem.</u> <u>36</u> (11) 1580-1596 (1993).)

Example 13

(-)-9,10-Difluoro-2,3-dihydro-3(S)-methyl-7-oxo-7H-pyrido[1,2,3-de]-1,4-benzox-aine-6-carboxylic acid <u>56</u> is prepared from (+)-Ethyl 2-(2-methoxy-3,4,5-trifluorobenzoyl)-3-[(1-

acetoxyprop-2(S)-yl)amino]acrylate <u>54</u> by first doing Step d as in Example 1, followed by refluxing the resulting reaction mixture with a 10% aq. KOH solution.

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The cyclization precursor <u>54</u> is prepared from 2-methoxy-3,4,5-trifluorobenzoyl chloride <u>51</u> as shown by using literature procedures. (See E.g., in <u>Heterocycles</u> <u>45</u> (1), 137-145 (1997).)

# Example 14

Ethyl ester of oxolinic acid <u>61</u> is prepared by a process similar to that of Example 1 from 2-methoxy-4,5-(methylenedioxy)benzoic acid <u>57</u> as shown below. In Step c, ethylamine is used instead of cyclopropylamine.

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Example 15:

Ethyl-1-cyclopropyl-1,4-dihydro-8-methoxy-7-fluoroquinolone carboxylate <u>66</u> is prepared by a process similar to that of Example 1 from 4-fluoro-3-methoxy-2-phenylthio benzoic acid <u>62</u>. The benzoic acid <u>62</u> is prepared from 4-fluoro-3-methoxy benzoic acid <u>22</u> by a procedure similar to that disclosed in literature. (See, e.g., US Patent No. 5,334, 753, which is incorporated herein by reference.)

#### WHAT IS CLAIMED IS:

1. A process for making a compound having a structure according to Formula (I), or an optical isomer, diastereomer or enantiomer thereof, or a pharmaceutically-acceptable salt, hydrate, or biohydrolyzable ester, amide or imide thereof:

$$R^6$$
 $R^7$ 
 $A$ 
 $R^7$ 
 $R^7$ 
 $R^2$ 
 $R^3$ 
 $R^3$ 
 $R^3$ 
 $R^3$ 

the process comprising reacting one or more organosilicon reagents with a compound having a structure according to Formula (A):

$$R^{6}$$
 $R^{7}$ 
 $A$ 
 $XR^{9}$ 
 $R^{1}$ 
 $R^{1}$ 

wherein with regard to Formula (I) and Formula (A):

- (A) (1) A is N or C-R<sup>8</sup>, where R<sup>8</sup> is selected from hydrogen, C<sub>1</sub> to about C<sub>15</sub> alkyl, aryl, halo, a heterocyclic ring, amino, C<sub>1</sub> to about C<sub>15</sub> alkylamino, arylamino, C<sub>1</sub> to about C<sub>15</sub> alkoxy, nitro, cyano, aryloxy, esters of hydroxy, C<sub>1</sub> to about C<sub>15</sub> alkylthio, arylthio, aryloxy, esters of thio, C<sub>1</sub> to about C<sub>15</sub> alkylsulfonyl, arylsulfonyl, C<sub>1</sub> to about C<sub>15</sub> alkylphosphonyl, arylphosphonyl, C<sub>1</sub> to about C<sub>15</sub> alkylacyl, arylacyl, and aryl esters and amides of carboxy;
  - (2) R<sup>7</sup> is selected from hydrogen, C<sub>1</sub> to about C<sub>15</sub> alkyl, aryl, a heterocyclic ring, amino, C<sub>1</sub> to about C<sub>15</sub> alkylamino, arylamino, halo, nitro, cyano, C<sub>1</sub> to about C<sub>15</sub> alkoxy, aryloxy, esters of hydroxy, C<sub>1</sub> to about C<sub>15</sub> alkylthio, arylthio, esters of thio, C<sub>1</sub> to about C<sub>15</sub> alkylsulfonyl, arylsulfonyl, C<sub>1</sub> to about C<sub>15</sub> alkylphosphonyl, arylphosphonyl, C<sub>1</sub> to about C<sub>15</sub> alkylacyl, arylacyl, and C<sub>1</sub> to about C<sub>15</sub> alkyl and aryl esters and amides of carboxy;

- (3) R<sup>6</sup> is selected from hydrogen, halo, C<sub>1</sub> to about C<sub>15</sub> alkyl, aryl, a heterocyclic ring, amino, C<sub>1</sub> to about C<sub>15</sub> alkylamino, arylamino, nitro, cyano, alkoxy, aryloxy, esters of hydroxy, C<sub>1</sub> to about C<sub>15</sub> alkylthio, arylthio, esters of thio, C<sub>1</sub> to about C<sub>15</sub> alkylsulfonyl, arylsulfonyl, C<sub>1</sub> to about C<sub>15</sub> alkylphosphonyl, arylphosphonyl, C<sub>1</sub> to about C<sub>15</sub> alkylacyl, arylacyl, and C<sub>1</sub> to about C<sub>15</sub> alkyl and aryl esters and amides of carboxy;
- (4) R<sup>5</sup> is selected from hydrogen, C<sub>1</sub> to about C<sub>15</sub> alkyl, aryl, cyano, a heterocyclic ring, amino, C<sub>1</sub> to about C<sub>15</sub> alkylamino, arylamino, C<sub>1</sub> to about C<sub>15</sub> alkylacyl, arylacyl, and aryl esters and amides of carboxy;
- (5) R<sup>1</sup> is selected from a 3 to about 17 membered carbocyclic ring, a heterocyclic ring, C<sub>1</sub> to about C<sub>6</sub> alkyl, C<sub>1</sub> to about C<sub>6</sub> alkene, C<sub>1</sub> to about C<sub>6</sub> alkyne and -CH(R<sup>10</sup>)(R<sup>11</sup>) where R<sup>10</sup> is selected from C<sub>1</sub> to about C<sub>6</sub> alkyl and phenyl and R<sup>11</sup> is -CH<sub>2</sub>Y(O=)CR<sup>12</sup> where R<sup>12</sup> is selected from C<sub>1</sub> to about C<sub>6</sub> alkyl and phenyl and Y is selected from -NH-, -O- and -S-;
- (6) R<sup>2</sup> is selected from hydrogen, C<sub>1</sub> to about C<sub>15</sub> alkyl, aryl, a heterocyclic ring, C<sub>1</sub> to about C<sub>15</sub> alkylthio and arylthio; and
- (7) R<sup>3</sup> is selected from hydrogen, C<sub>1</sub> to about C<sub>15</sub> alkoxy, aryloxy, C<sub>1</sub> to about C<sub>15</sub> alkyl and aryl; or
- (B) R<sup>1</sup> and R<sup>2</sup> can join to form a 5- or 6-membered carbocyclic or heterocyclic ring, where A, R<sup>3</sup>, R<sup>5</sup>, R<sup>6</sup>, R<sup>7</sup> and R<sup>8</sup>, if present, are as described in (A); or
- (C) R<sup>6</sup> and R<sup>7</sup> can join to form a 5- or 6-membered carbocyclic or heterocyclic ring, where A, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>5</sup> and R<sup>8</sup>, if present, are as described in (A);

and wherein with regard to Formula (A):

- (D) X is selected from -O- and -S- and  $R^9$  is selected from  $C_1$ - $C_{10}$  alkyl, aryl and heteroaryl.
- 2. The process of Claim 1 wherein  $R^9$  in Formula (A) is selected from  $C_1 C_4$  alkyl and phenyl; preferably  $R^9$  is selected from unsubstituted  $C_1 C_2$  alkyl and unsubstituted phenyl
- 3. The process of Claim 1 wherein  $R^9$  in Formula (A) is selected from  $C_1 C_4$  alkoxy, thio ( $C_1 C_4$ ) alkyl, amyloxy and thioaryl; preferably  $R^9$  is selected from methoxy, ethoxy, propoxy,  $SCH_3$ ,  $-SCH_2CH_3$ ,  $-SCH_2CH_3$ , phenoxy and  $-S(C_6H_5)$ .

- 4. The process of any of Claims 1-3 wherein none of  $R^1$ ,  $R^2$ ,  $R^6$ , or  $R^7$  join together to form a ring fused to the A-containing or N'-containing rings.
- 5. The process of any of Claims 1-3 wherein  $R^1$  and  $R^2$  join to form a 5- or 6-membered carbocyclic or heterocyclic ring.
- 6. The process of any of Claims 1-3 wherein  $R^6$  and  $R^7$  join to form a 5- or 6-membered carbocyclic or heterocyclic ring.
- 7. A process for making a compound having a structure according to Formula (I), or an optical isomer, diastereomer or enantiomer thereof, or a pharmaceutically-acceptable salt, hydrate, or biohydrolyzable ester, amide or imide thereof:

$$R^5$$
  $R^5$   $R^3$   $R^7$   $R^2$   $R^2$   $R^3$ 

the process comprising reacting one or more organosilicon reagents with a compound having a structure according to Formula (A):

$$R^{6}$$
 $R^{7}$ 
 $A$ 
 $XR^{9}$ 
 $R^{1}$ 
 $H$ 
 $(A)$ 

wherein with regard to Formula (I) and Formula (A):

- (A) (1) A is N or C-R<sup>8</sup>, where R<sup>8</sup> is selected from hydrogen, halo, about C<sub>1</sub>-C<sub>4</sub> alkyl, phenyl, about C<sub>1</sub>-C<sub>4</sub> alkoxy, about C<sub>1</sub>-C<sub>4</sub> alkylthio, and phenoxy;
  - (2) R<sup>7</sup> is selected from hydrogen, halo, nitro, C<sub>1</sub> to about C<sub>4</sub> alkyl, unsubstituted amino, C<sub>1</sub> to about C<sub>4</sub> mono- or di-alkylamino, phenyl, naphthyl, a heterocyclic ring having one ring with 5 or 6 ring atoms or two fused rings with 8-10 ring atoms, C<sub>1</sub> to about C<sub>4</sub> alkylthio, phenylthio, phenoxy and C<sub>1</sub> to about C<sub>4</sub> esters of hydroxy;

PCT/US01/48536

- (3) R<sup>6</sup> is selected from hydrogen, halo, nitro, C<sub>1</sub> to about C<sub>4</sub> alkylamino, C<sub>1</sub> to about C<sub>4</sub> alkoxy, and C<sub>1</sub> to about C<sub>4</sub> esters of hydroxy;
- (4) R<sup>5</sup> is selected from hydrogen, halo, C<sub>1</sub> to about C<sub>4</sub> alkyl, phenyl, amino and C<sub>1</sub> to about C<sub>4</sub> mono- or dialkylamino;
- (5) R<sup>1</sup> is selected from C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>3</sub>-C<sub>6</sub> cycloalkyl and aryl.
- (6) R<sup>2</sup> is selected from hydrogen, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkylthio and phenyl; and
- (7) R<sup>3</sup> is selected from hydrogen, about C<sub>1</sub>-C<sub>4</sub> alkoxy and phenoxy;

and wherein with regard to Formula (A):

- (B) X is selected from -O- and -S- and R<sup>9</sup> is selected from unsubstituted methyl, ethyl and phenyl.
- 8. The process of any of Claims 1-7 wherein the molar ratio of the organosilicon reagent to the compound of Formula (A) is from 0.5:1 to 12:1, more preferably from 1:1 to 4:1.
- 9. The process of any of Claims 1 8 wherein:
  - (A) the organosilicon reagent is selected from the group consisting of chlorotrimethylsilane, N,O-bis(trimethylsilyl)acetamide, N,O-bis(trimethylsilyl)trifluoroacetamide, 1,3-bis(trimethylsilyl)urea, 1,1,1,3,3,3-hexamethyldisilazane, N-methyl-N-trimethylsilyltrifluoroacetamide, 1-trimethylsilylimidazole, trimethylsilyl trifluoromethanesulfonate, tert-butyldimethylchlorosilane, 1-(tert-butyldimethylsilyl)imidazole, ethyl(trimethylsilyl)acetate, N-tert-butyldimethyl-N-methyltrifluoroacetamide, tert-butyldimethylsilyl trifluoromethanesulfonate, tert-butyldiphenylchlorosilane, tert-butylmethoxyphenylbromosilane, dimethylphenylchlorosilane, triethylchlorosilane, triethylsilyl trifluoromethane-sulfonate, and triphenylchlorosilane, and mixtures thereof; preferably the organosilicon reagent is selected from N,O-bis(trimethylsilyl)acetamide, N,O-bis(trimethylsilyl)trifluoroacetamide, N-methyl-N-trimethylsilyltrifluoroacetamide and tert-butyldiphenylchlorosilane, and mixtures thereof;

- (B) the organosilicon reagent and the compound of Formula (A) are reacted at a temperature of from -50°C to 250°C; preferably from -10°C to 160°C; more preferably from 20°C to 140°C; and
- (C) the organosilicon reagent and the compound of Formula (A) are reacted at a pressure of from 0.5 atm to 50 atm; preferably 0.8 atm to 10 atm; more preferably from 1 atm to 2 atm.
- 10. The process of any of Claims 1 9 wherein the organosilicon reagent and the compound of Formula (A) are reacted in a solvent selected from acetonitrile, N-methylpyrrolidinone (NMP), dimethylformide, N,N-dimethylacetamide, toluene, xylene, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, diglyme; more preferred solvents include acetonitrile, toluene, NMP, and mixtures of any of the foregoing.

### INTERNATIONAL SEARCH REPORT

Inte il Application No PCT/US 01/48536

A. CLASSIFICATION OF SUBJECT MATTER IPC 7 CO7D215/56 CO7U C07D471/04 C07D498/06 C07D513/04 C07D401/04 According to International Patent Classification (IPC) or to both national classification and IPC B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) IPC 7 CO7D Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched Electronic data base consulted during the international search (name of data base and, where practical, search terms used) WPI Data, EPO-Internal C. DOCUMENTS CONSIDERED TO BE RELEVANT Relevant to claim No. Citation of document, with indication, where appropriate, of the relevant passages Category \* 1-10 US 5 703 231 A (GODLEWSKI JANE ELLEN ET X AL) 30 December 1997 (1997-12-30) cited in the application Claim 1, examples column 24, line 21 - line 22 1-10 WO 96 04286 A (PROCTER & GAMBLE) X 15 February 1996 (1996-02-15) Claim 1, examples WO 96 04247 A (PROCTER & GAMBLE) 1-10 X 15 February 1996 (1996-02-15) Claim 1, examples Patent family members are listed in annex. Further documents are listed in the continuation of box C. Special categories of cited documents: "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the A document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone filing date document which may throw doubts on priority claim(s) or which is clied to establish the publication date of another citation or other special reason (as specified) document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such docudocument referring to an oral disclosure, use, exhibition or ments, such combination being obvious to a person skilled other means document published prior to the international filing date but later than the priority date claimed "&" document member of the same patent family Date of mailing of the international search report Date of the actual completion of the international search 09/04/2002 2 April 2002 Name and mailing address of the ISA Authorized officer European Patent Office, P.B. 5818 Patentiaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016 Fritz, M

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